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SYNTHESIS OF ORGANIC COMPOUNDS FOR
MALARIA CHEMOTHERAPEUTIC STUDIES

ANNUAL PROGRESS REPORT

by

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

During the present report period, 40 compounds of the following categories have been synthesized, characterized, and submitted for antimalarial evaluation: (a) compounds having a triangular structural feature common to many causal prophylactic antimalarial agents; (b) α,β-unsaturated amino acids and related derivatives; (c) compounds related to the antimalarial antibiotic furanomycin; and (d) deazafebrifugine and related compounds. 8-(6-Amino-3-hexylamino)-6-methoxy-4-methylquinoline diphosphate (WR-215761) exhibited outstanding antimalarial activity against P. berghei.

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FOREWORD

This annual report was prepared at Midwest Research Institute under Contract No. DADA-49-193-MD-2749 with the U.S. Army Medical Research and Development Command.

The period of research covered in this report is from 1 August 1974 to 31 July 1975. The work was carried out under the direction of Dr. C. C. Cheng, Principal Investigator. The synthetic work was performed by Mr. William H. Burton, Dr. Ping-Lu Chien, and Dr. Shou-Jen Yan.

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I. INTRODUCTION

This is the Tenth Annual Progress Report from Midwest Research Institute under Contract No. DADA-49-193-MD-2749 with the U.S. Army Medical Research and Development Command on preparation of organic compounds as potential antimalarial drugs.

During the present report period, we have studied the synthesis and characterization of compounds of the following categories: (a) compounds having a triangular structural feature common to many causal prophylactic antimalarial agents; (b) α,β-unsaturated amino acids and related derivatives; (c) compounds related to the antimalarial antibiotic furanomycin; and (d) deazafebrifugine and related compounds. A total of 40 compounds have been synthesized, characterized, and submitted for antimalarial evaluation.

II. RESULTS AND DISCUSSION

A. Compounds Containing a Common Triangular Causal Prophylactic Antimalarial Structural Feature

Preparation of several compounds conforming to a triangular structural feature common to many prophylactic antimalarial agents[1,2] was conducted.

N^1,N^1-Diethyl-N^4-(3,4-dimethoxyphenyl)-1,4-pentanediamine (A-3) was prepared in one step by the platinum-catalyzed reductive alkylation reaction of 4-nitroveratrole (A-1) and 5-diethylamino-2-pentanone (A-2) in good yield.
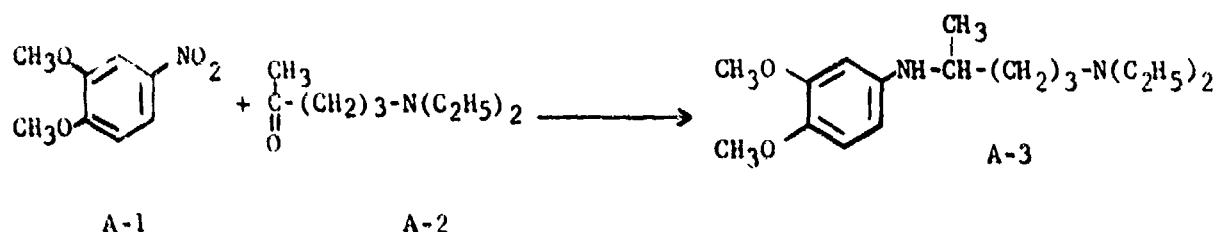
4-Bromo-5-[(5-diethylamino-2-pentyl)amino]veratrole (A-9), an RC-12 analog, was synthesized from veratrole (A-4) according to the following scheme.
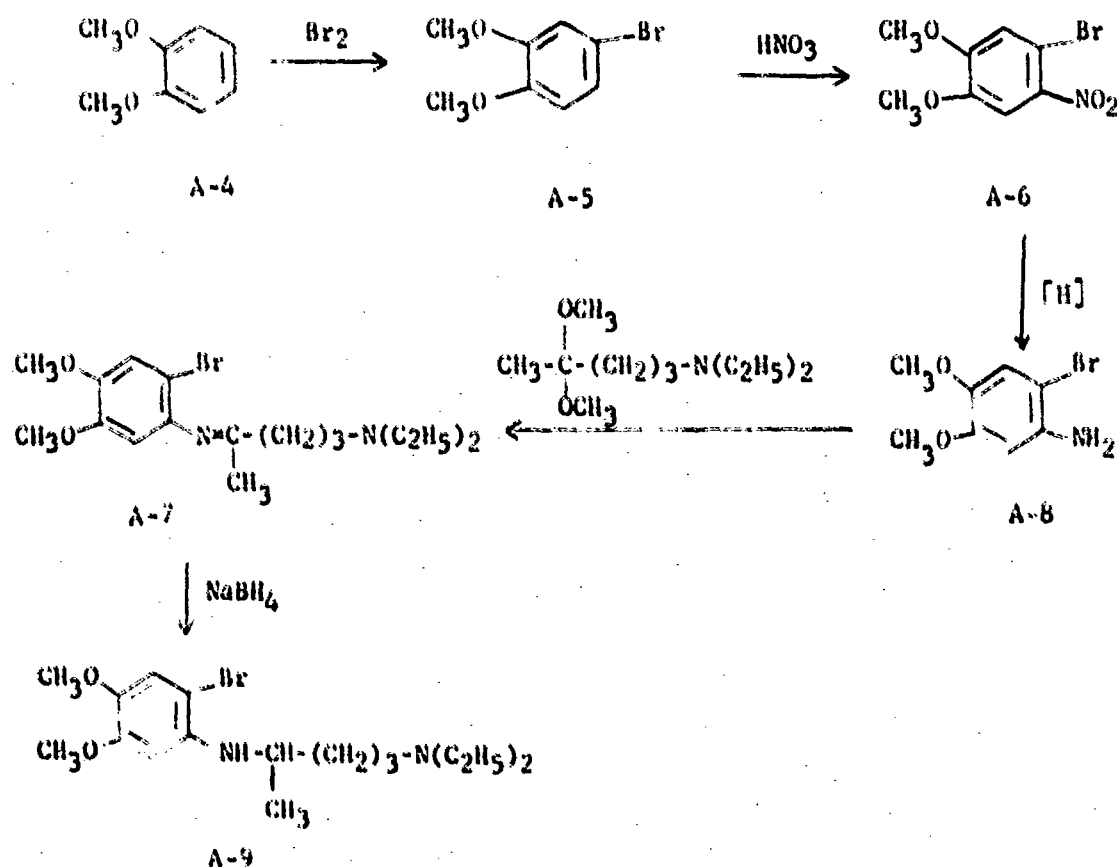
Bromination[3] of veratrole (A-4) followed by nitration[4] of the intermediate A-5 gave 4-bromo-5-nitroveratrole (A-6). The latter was hydrogenated in the presence of 5% Pt/C to yield 2-bromo-4,5-dimethoxyaniline (A-11). Condensation of A-11 with 5-diethylamino-2,2-dimethoxypentane in the presence of p-toluenesulfonic acid yielded the anil A-12, which was reduced with $NaBH_4$ to give the target compound A-13.
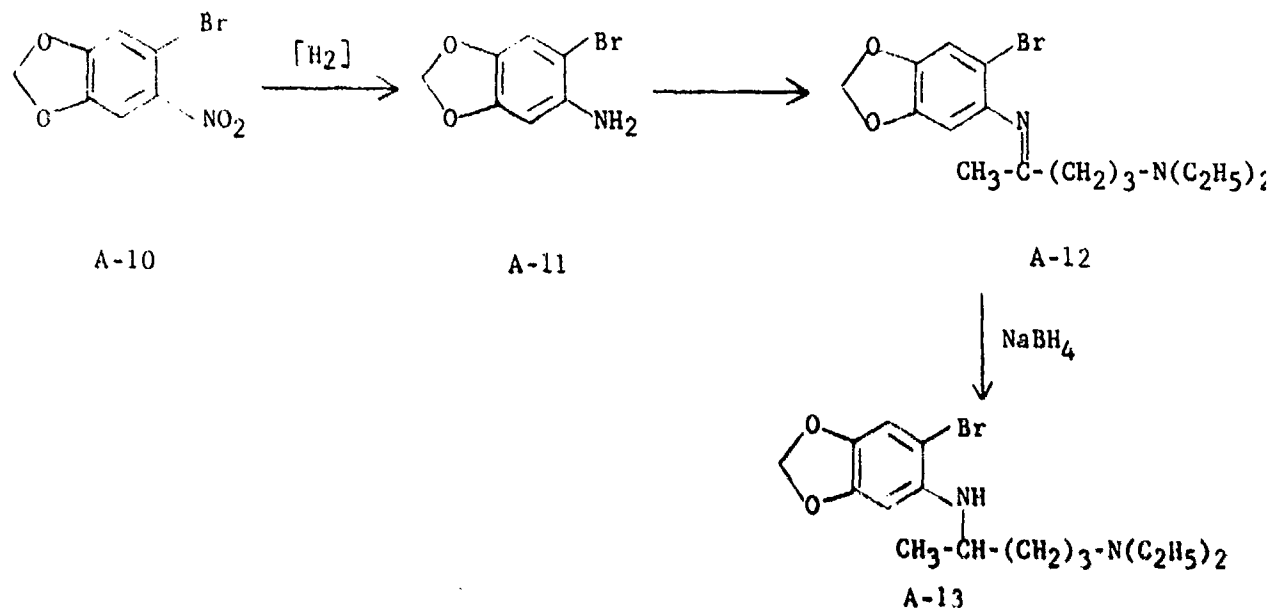
2-Bromo-4,5-methylenedioxy-N-(5-diethyl-aminopentyl)aniline (A-13), was synthesized from 2-bromo-4,5-methlenedioxy-nitrobenzene (A-10) by the following route.

A-10   A-11   A-12

A-13

Compound A-10 was smoothly reduced to 2-bromo-4,5-methylenedioxy-aniline (A-11) in benzene using platinum-on-carbon as the catalyst. Condensation of A-11 with 5-diethylamino-2,2-dimethoxypentane afforded the anil A-12, which was then reduced to the desired target compound A-13 with sodium borohydride.

Since the chloro-substituted amine A-15[5] will be needed for the preparation of some compounds in this area, the aminoketone A-2 was reduced with RED-AL to the alcohol A-14;[6] the latter was treated with thionyl chloride to give A-15 as a HCl salt in an overall yield of 52%.

A-14   A-15
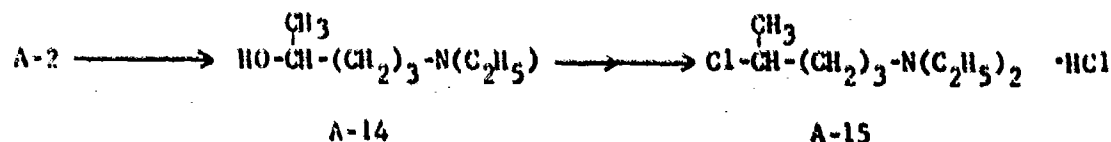
6-[(5-Diethylamino-2-pentyl)amino]quinoxaline (A-21) was prepared as follows: Condensation of 4-nitro-o-phenylenediamine (A-16) with glyoxal-sodium bisulfite adduct[7] yielded 8-nitroquinoxaline[8] (A-17). Reduction of A-17 with stannous chloride[9] gave the corresponding 8-amino derivative A-18. The latter was condensed with 5-diethylamino-2,2-dimethoxypentane[10] (A-19), and the resulting anil A-20 was reduced with sodium borohydride to yield the desired product A-21.

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A-16   A-17   A-18

A-19   A-20

A-21
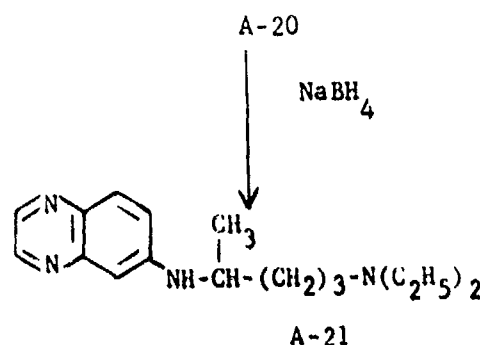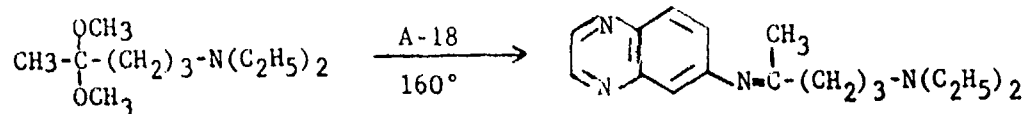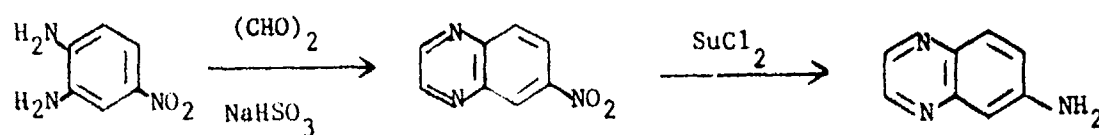
6-Methoxy-7-[(5-diethylamino-2-pentyl)amino]quinoxaline (A-28) was synthesized as follows. Treatment of 2-methoxy-5-nitroaniline (A-22) (Aldrich) with AcOH and Ac$_2$O followed by addition of red fuming HNO$_3$ gave the dinitro compound A-23.[11/] Catalytic hydrogenation of A-23 at 40 psig in MeOH afforded the amino compound A-24. The latter, without purification, was immediately converted to the quinoxaline A-25 with glyoxal disodium bisulfite. Compound A-25 was hydrolyzed with 5N HCl. The resulting aminoquinoxaline A-26 was coupled with 5-dimethylamino-2,2-dimethoxypentane (A-19) to give A-27, which was reduced with NaBH$_4$ in EtOH to yield the title compound A-28.

A-22   A-23   A-24

A-27 ← A-19   A-26   A-25

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$\xrightarrow{\text{A-19}}$

[Structure A-27: quinoxaline with OCH$_3$ and N=C(CH$_3$)-(CH$_2$)$_3$-N(C$_2$H$_5$)$_2$ substituent]

$\xrightarrow{\text{NaBH}_4}$

[Structure A-28: quinoxaline with OCH$_3$ and NH-CH(CH$_3$)-(CH$_2$)$_3$-N(C$_2$H$_5$)$_2$ substituent]

A-27   A-28
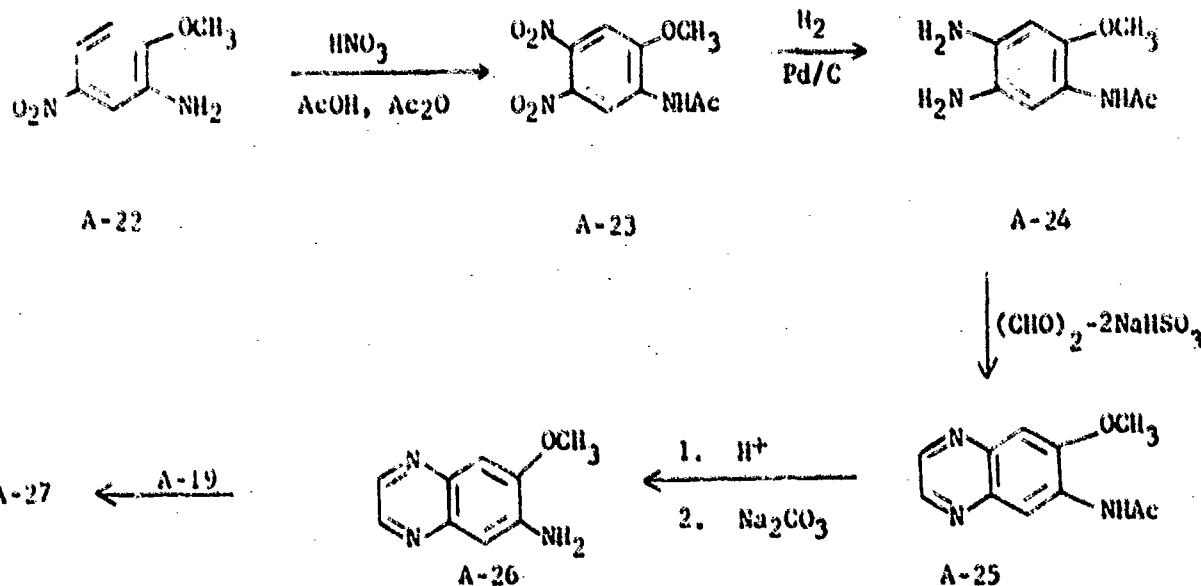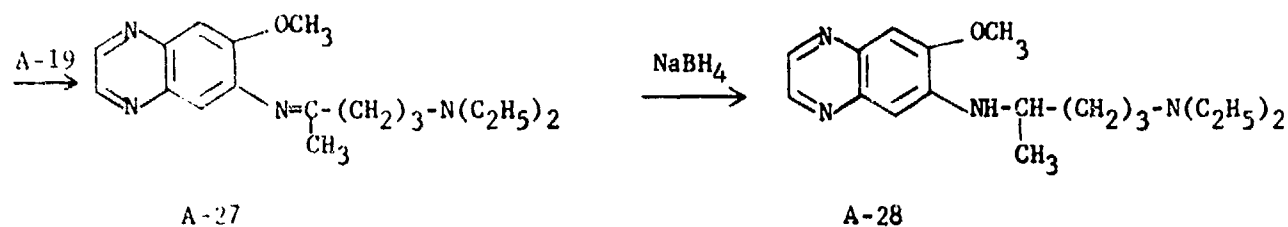
Attempts to synthesize target compounds A-35a and A-35b have been conducted by the following route. Acetylation of 4-methoxy-2-nitro-aniline (A-29) with Ac$_2$O and AcOH[12] gave A-30. Reduction of A-30 with iron in AcOH and H$_2$O yielded 2-amino-4-methoxyacetanilide[13] (A-31). The latter was condensed with 4-diethylamino-2,2-dimethoxypentane (A-19) to give the anil A-32, which was reduced to A-33 with NaBH$_4$. Hydrolysis of A-33 to A-34 is in progress.

[Structure A-29: benzene with CH$_3$O, NO$_2$, NH$_2$]
$\xrightarrow{\text{Ac}_2\text{O}}$
[Structure A-30: benzene with CH$_3$O, NO$_2$, NHAc]
$\xrightarrow[\text{AcOH}]{\text{Fe}}$
[Structure A-31: benzene with CH$_3$O, NH$_2$, NHAc]

A-29   A-30   A-31

$\downarrow$ A-19

[Structure A-32: CH$_3$O-benzene with N=C(CH$_3$)-(CH$_2$)$_3$-N(C$_2$H$_5$)$_2$ and NHAc]

[Structure A-33: CH$_3$O-benzene with NH-CH(CH$_3$)-(CH$_2$)$_3$-N(C$_2$H$_5$)$_2$ and NHAc]
$\xleftarrow{\text{NaBH}_4}$

A-33   A-32

$\downarrow$ [H$_2$O]

[Structure A-34: CH$_3$O-benzene with NH-CH(CH$_3$)-(CH$_2$)$_3$-N(C$_2$H$_5$)$_2$ and NH$_2$]

A-34

[Reagent: X-C$_6$H$_4$-C(OCH$_3$)(CH$_3$)(OCH$_3$)]
$\xrightarrow{}$
[Structure A-35: CH$_3$O-benzene with NH-C(CH$_3$)-(CH$_2$)$_3$-N(C$_2$H$_5$)$_2$ and N=C(CH$_3$)-C$_6$H$_4$-X]

A-35a. X = Cl
    b. X = CH$_3$

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For the synthesis of the target compound A-39, a different approach starting with 4-hydroxy-3-nitroaniline (A-39) has been studied. The introduction of the dialkylaminoalkylamino side chain was readily achieved, but again the hydrolysis of the acetamido protecting group in compound A-37 presented difficulty.

HO—[ring]—O_2N / NH_2 **A-36** → HO—[ring]—O_2N / NH-CO-CH$_3$ —(CH_3I / DMF)→ CH_3O—[ring]—O_2N / NH-CO-CH$_3$

↓ H_2/Pd

CH_3O—[ring]—H_2N / NH-CO-CH$_3$

→ CH_3O—[ring]— N / NH-$\overset{O}{\overset{\|}{C}}$-CH$_3$; CH$_3$-C-(CH$_2$)$_3$-N(C$_2H_5$)$_2$

↓

CH_3O—[ring]— HN / NH-CO-CH$_3$; CH$_3$-CH-(CH$_2$)$_3$-N(C$_2$H$_5$)$_2$ **A-37**

—(H_2O / HCl)→ CH_3O—[ring]— HN / NH$_2$; CH$_3$-CH-(CH$_2$)$_3$-N(C$_2$H$_5$)$_2$

↓ CH$_3$-C(OCH$_3$)(OCH$_3$)—[ring]—Cl **A-38**

CH_3O—[ring]— HN / N=C-$\overset{CH_3}{}$—[ring]—Cl ; CH$_3$-CH-(CH$_2$)$_3$-N(C$_2$H$_5$)$_2$

A-39
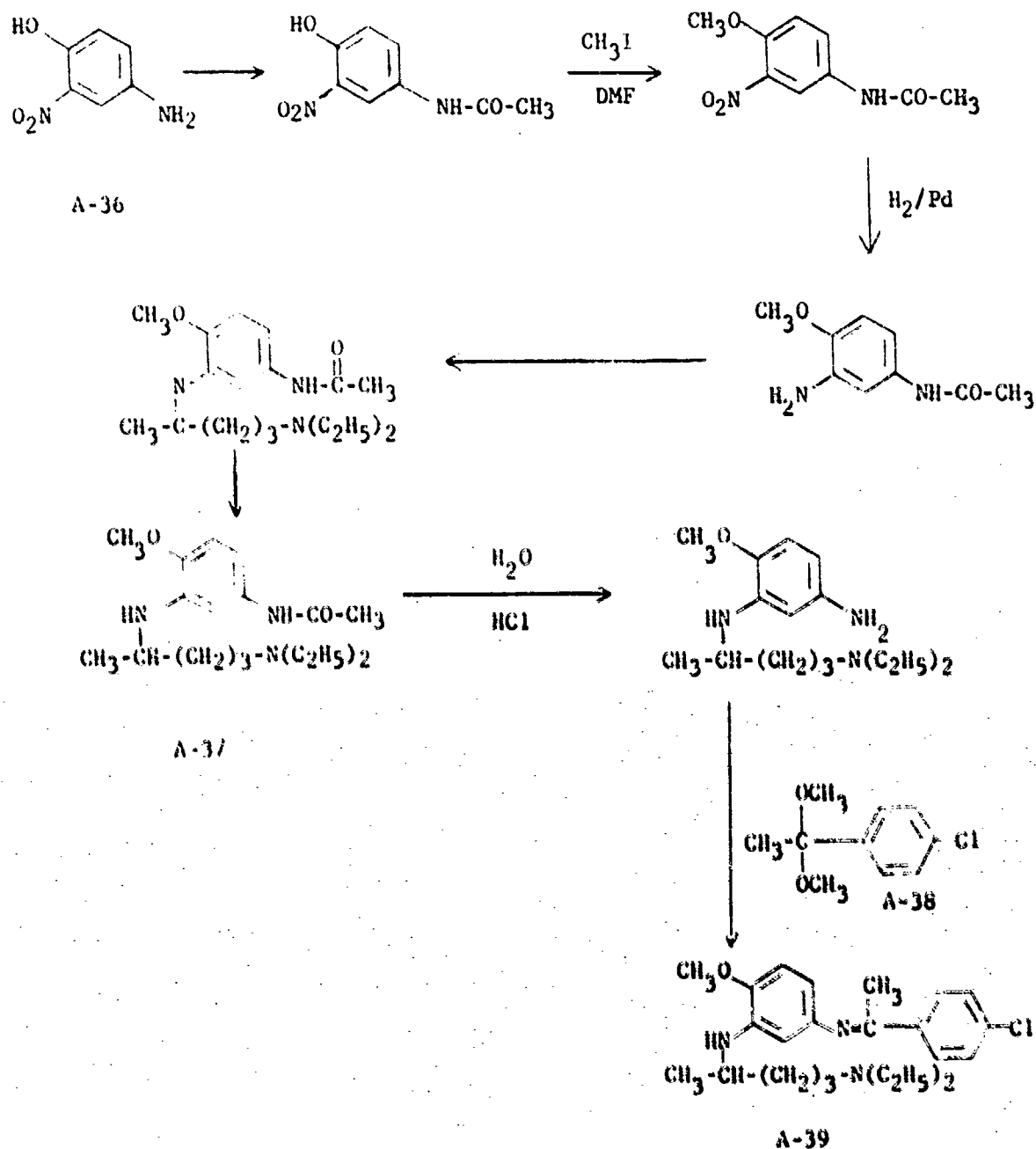
In the second approach, the commercially available 2-methoxy-5-nitroaniline (A-40) was used as the starting material. In this approach, the dialkylaminoalkyl side chain was to be attached to the amino group first.

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A convenient method through the formation of the Schiff base intermediate A-43 followed by reduction was therefore attempted. Under the usual reaction conditions, the ketal A-41 did react with the compound A-40, but the nitro group apparently also participated in the reaction, resulting in the formation of an intractable material. The parent ketone A-42 did not react with the amino group of A-40 under various conditions. Direct alkylation of A-40 with the bromophthalimide derivative A-44 was then carried out in an autoclave to give a low yield of the desired product A-45, which was catalytically reduced to the corresponding amino compound A-46. On reaction with p-chloroacetophenone dimethyl ketal; it also gave a highly complex mixture of products, from which the desired compound A-47 could not be isolated. p-Chloroacetophenone itself, again, does not react with the amino group of A-46 to form the Schiff base.

7
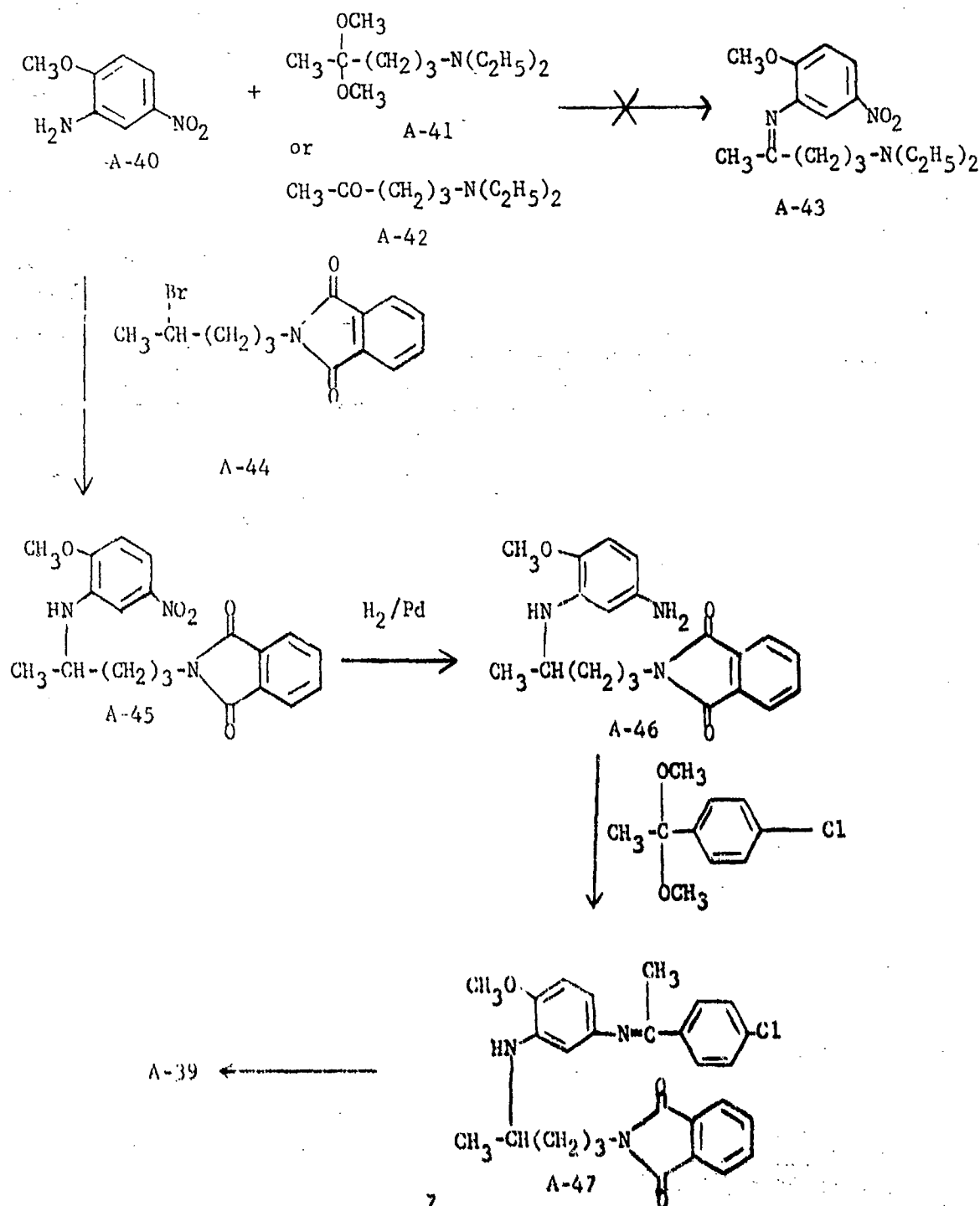
These failures necessitated us to study another route, in which the required imino side chain was to be attached before the introduction of the dialkylaminoalkylamine function. The Schiff base A-50 was readily prepared from the starting material A-40 in three steps, but, unfortunately, the protecting acetamido group could not be completely hydrolyzed to the amino function by boiling in 50% aqueous KOH in EtOH. Even the trifluoro-acetamido compound was found to be vr y resistant to base hydrolysis. Under more drastic conditions, i.e   y using ethylene glycol as solvent, the hydrolysis went much faster,   the product formed during hydrolysis decomposed rapidly, apparently du_ to facile oxidation of the o-aminophenol ether system, as nmr spectrum clearly showed the disappearance of the OCH3 group.

A-40

A-48 a. R=CH$_3$
      b. R=CF$_3$

A-49 a. R=CH$_3$
      b. R= $_3$
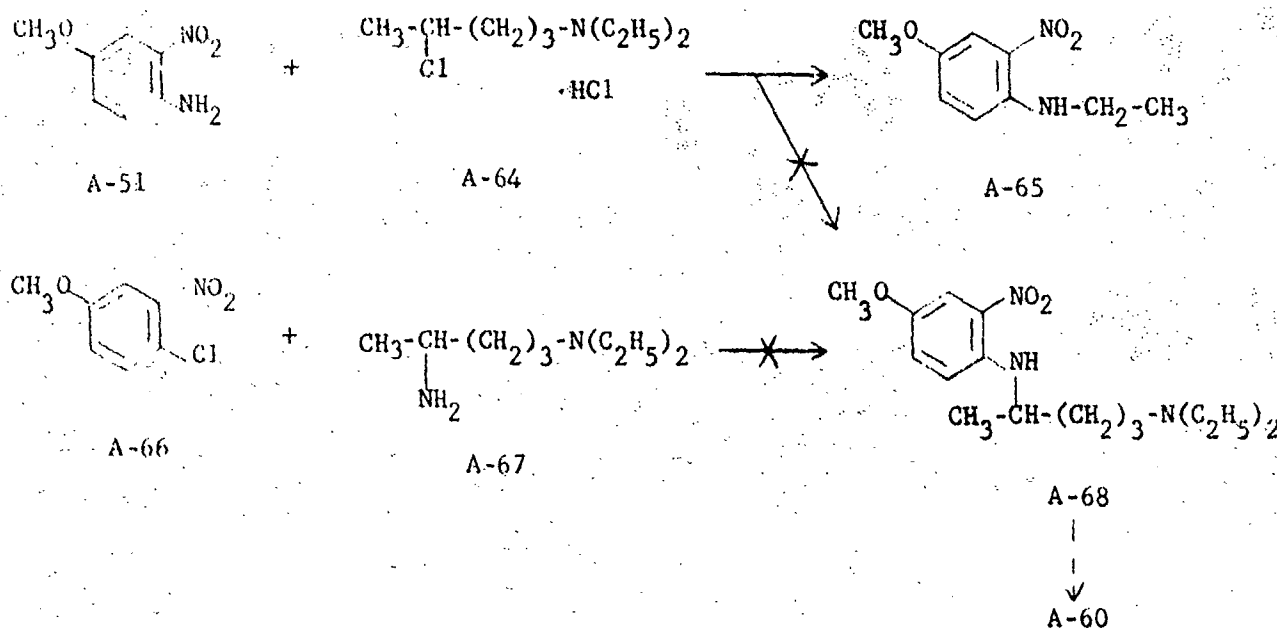
A-50 a. R=CH$_3$
      b. R=CF$_3$
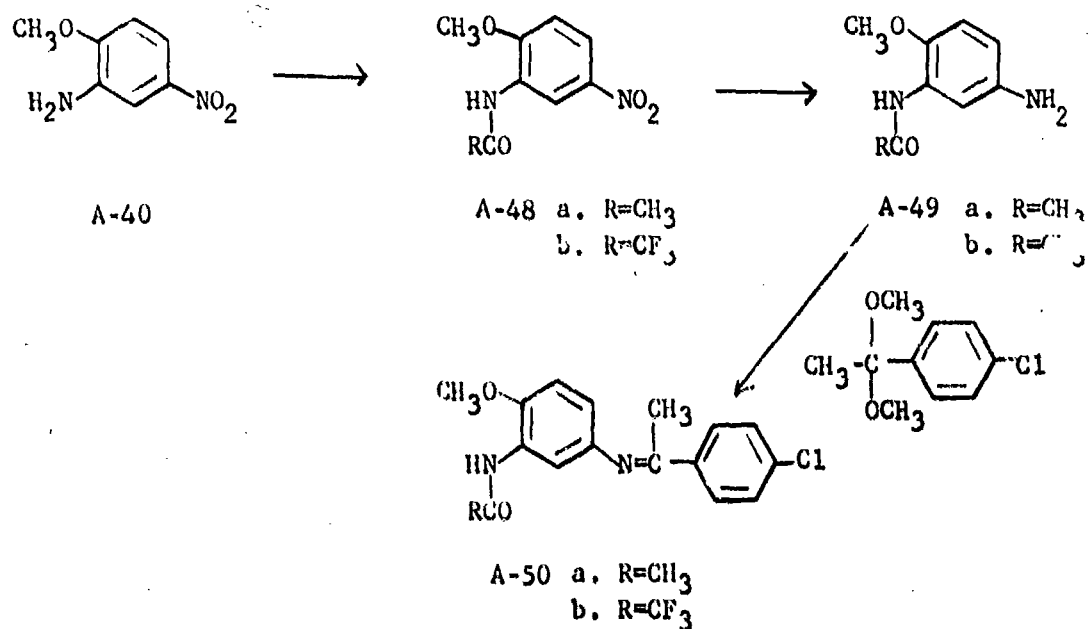
Synthesis of another target compound, 1-(5-diethylamino-2-pentyl)-5-methoxybenzimidazole (A-60), was initially studied according to the following reaction schemes.

8

9
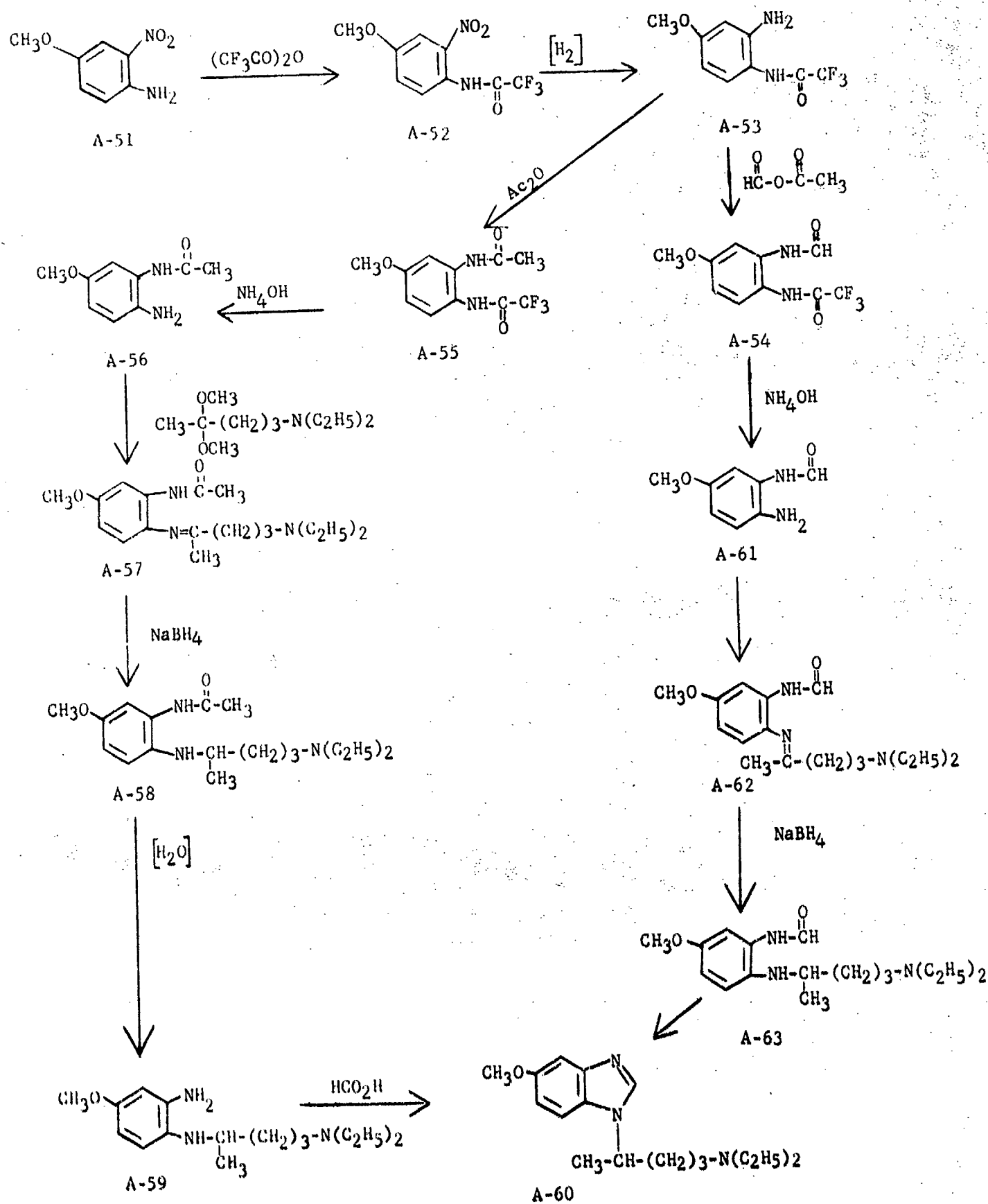
The amino group of 4-methoxy-2-nitroaniline was protected by a trifluoroacetyl group to give A-52, which was reduced catalytically to yield A-53. From compound A-53, there are two possible routes to the target compound A-60, and both routes have been studied. Formylation of A-53 was achieved with acetic formic anhydride prepared in situ according to a literature method.[14/] The formylated product A-54 precipitated almost immediately upon the addition of A-53 to the mixed anhydride solution. Compound A-54, collected as a white solid, m.p. 190°, had two carbonyl absorption bands. The corresponding acetylated product A-55 was also obtained as a white solid. Hydrolysis of A-55 with ammonium hydroxide in aqueous ethanol at 50° for 30 min gave the deacylated compound A-56, which was difficult to purify. Condensation of A-56 with 2,2-dimethoxy-5-diethylaminopentane (A-19) gave a liquid A-57 (ir: 1600-1690 cm^{-1}), which was dissolved in ethanol and stirred with $NaBH_4$ to yield an oily material A-58, the ir spectrum of which had peaks at 1660-1690 cm^{-1}. An attempt to hydrolyze the acetyl group of A-58 by refluxing with 5 N HCl for 4 hr and an attempt to form the benzimidazole ring by refluxing the resulting product with formic acid afforded only a small amount of oily material, which has not yet been characterized.
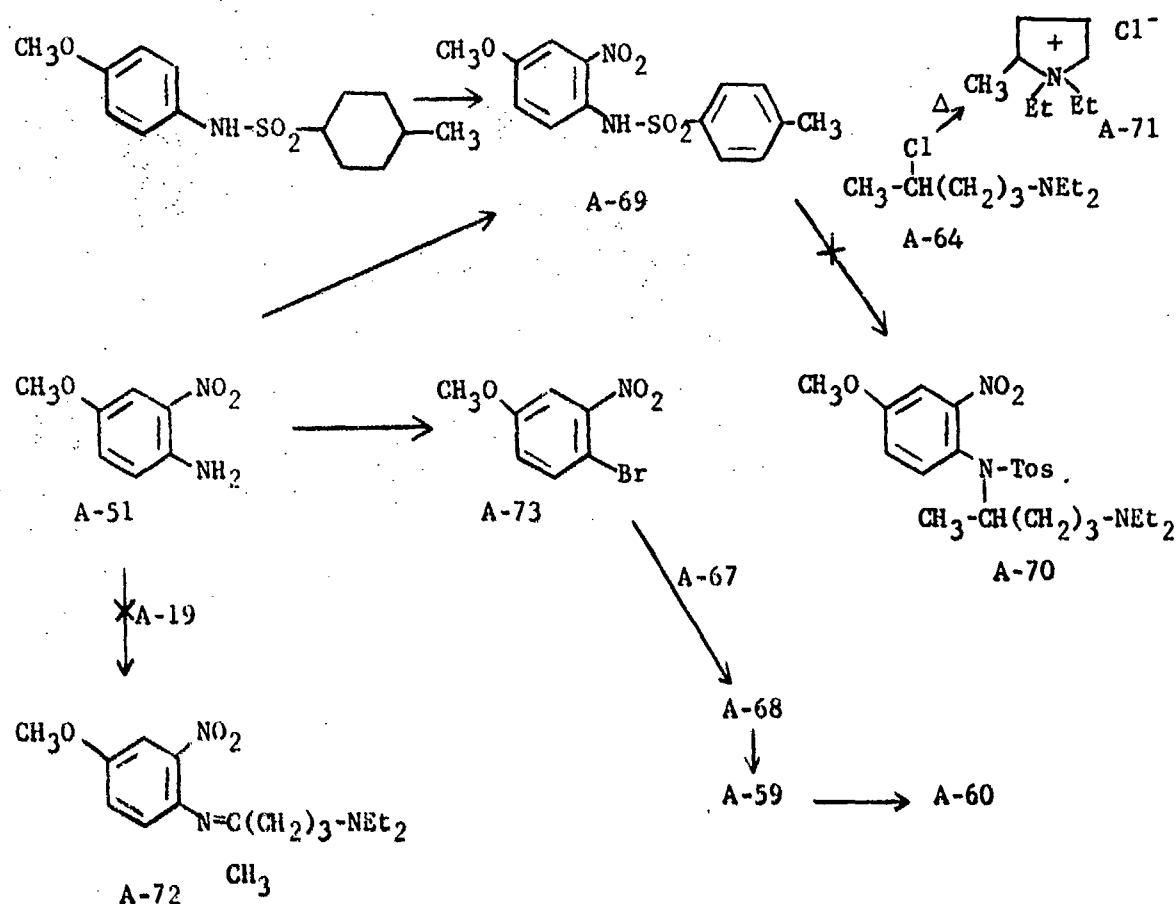
Another route via the formylated compound A-54 was also studied. Hydrolysis of A-54 with aqueous ammonia in aqueous ethanol at room temperature for 1 day yielded only a small amount of dark red oil which was difficult to purify.

Preparation of N-(5-diethylamino-2-pentyl)-4-methoxy-2-nitro-aniline (A-68) by the treatment of 2-nitro-p-anisidine (A-51) with 2-chloro-5-diethylaminopentane hydrochloride (A-64) was subsequently studied. When A-64 and two equivalents of A-51 were heated in 95% ethanol in a steel bomb at 170° for 16 hr, a product isolated through column chromatography on alumina was not the desired A-68 but rather 4-methyl-2-nitro-N-ethylaniline (A-65) according to its nmr spectrum. Preparation of A-68 by the treatment of 4-chloro-3-nitroanisole (A-66) with two equivalents of 2-amino-5-diethyl-amino-pentane (A-67) either at 170-200° in a steel bomb for 20 hr or at lower temperature and longer reactions times using DMF as solvent was also without success.
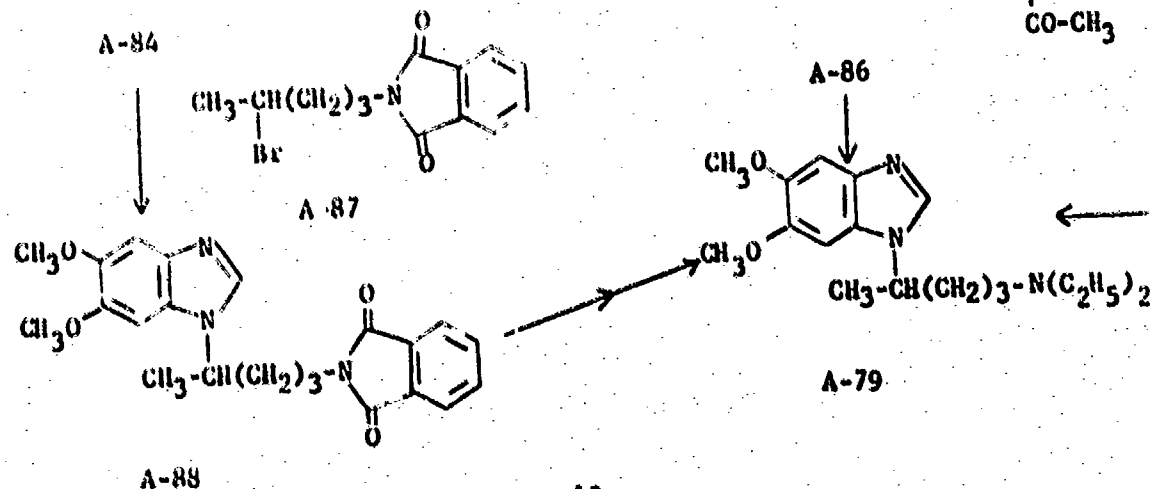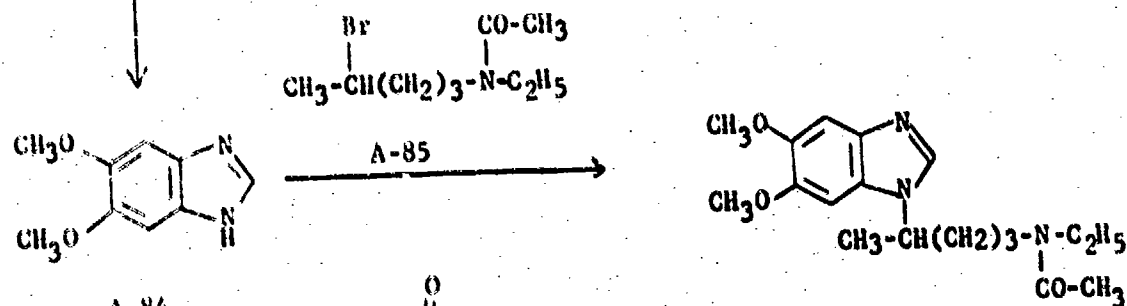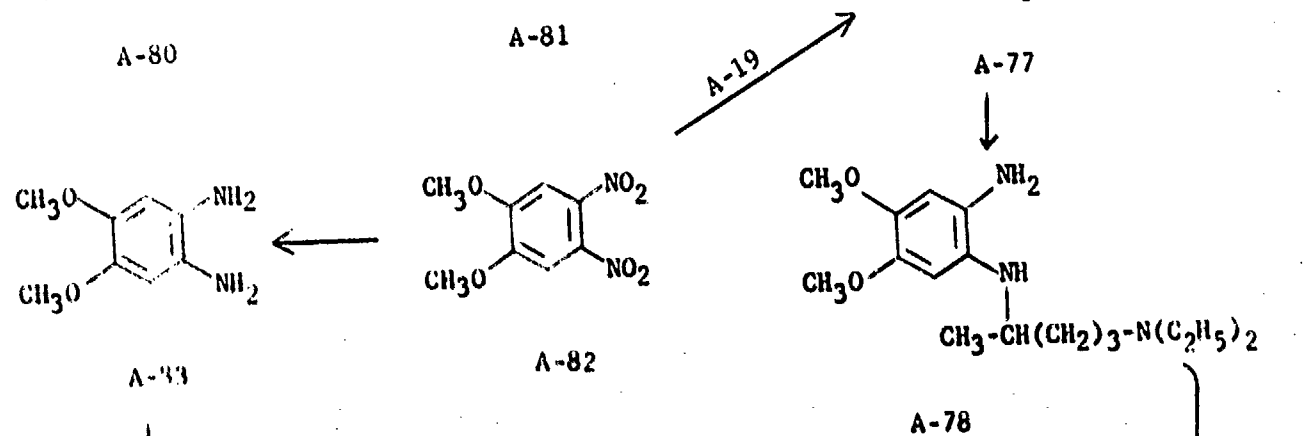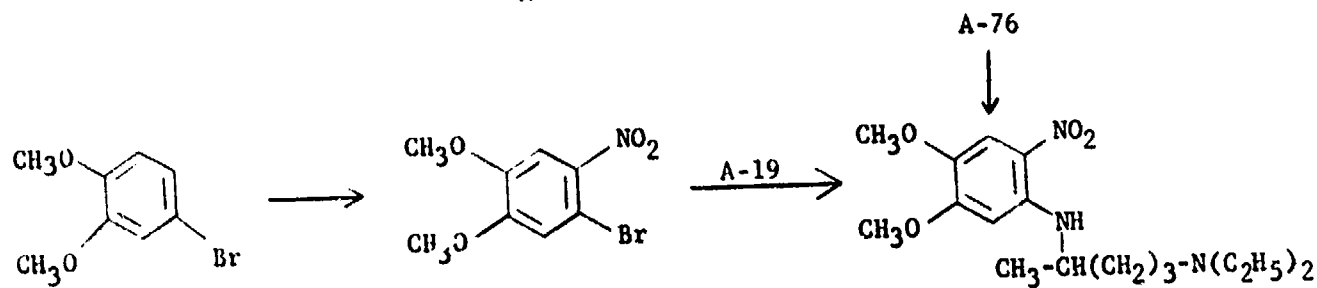
CH₃O—(ring)—NO₂ / NH₂ **A-51** + CH₃-CH-(CH₂)₃-N(C₂H₅)₂ / Cl ·HCl **A-64** → CH₃O—(ring)—NO₂ / NH-CH₂-CH₃ **A-65**

CH₃O—(ring)—NO₂ / Cl **A-66** + CH₃-CH-(CH₂)₃-N(C₂H₅)₂ / NH₂ **A-67** —✗→ CH₃O—(ring)—NO₂ / NH—CH₃-CH-(CH₂)₃-N(C₂H₅)₂ **A-68**
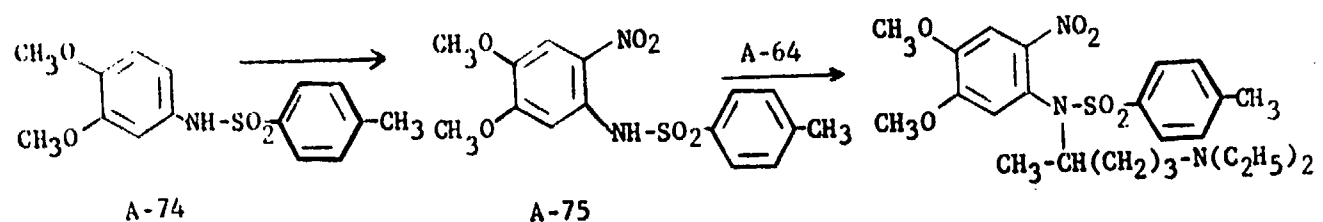
A-68
|
↓
A-60

Another approach to the synthesis of the target compound A-60
was to use the tosylated anisidine[16] as the starting material. Nitration
of A-61 in acetic acid gave a good yield of the nitrotosylate A-69.[17] The
latter was also prepared in better yield by direct tosylation of 2-nitro-p-
anisidine (A-51). Treatment of the sodium salt of A-69 in ethanol with a
concentrated ether solution of 4-chloro-N,N-diethylpentylamine (A-64, the
free base of A-15), according to the procedure of King et al.[18] for the
preparation of an analogous compound, failed to yield the desired product
A-70, presumably due to the instability of A-64. Attempts to isolate and
purify A-64 by distillation resulted in a quantitative conversion of A-64
to the corresponding cyclized pyrrolidine salt A-71.

Although the dimethyl ketal A-19 condensed with p-anisidine to
form a Schiff's base, it did not condense with A-51 to give A-72, presumably
due to the presence of the o-nitro function. Presently it is planned to
prepare A-60 by carrying out a reaction between 4-bromo-3-nitroanisole[19]
(A-73) with novoldiamine (A-67) according to the general procedure of Clemo
and Swan[20] followed by reduction and cyclization. Compound A-73 was pre-
pared from A-51 through the diazonium salt in 50% yield.

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CH_3O—⟨ ⟩—NH-SO_2—⟨cyclohexane⟩—CH_3 → CH_3O—⟨ NO_2 ⟩—NH-SO_2—⟨ ⟩—CH_3 **A-69**

$\overset{\Delta}{\longrightarrow}$ pyrrolidinium CH_3, Et, Et, N^+, Cl^- **A-71**

Cl—CH_3-$CH(CH_2)_3$-NEt_2 **A-64**

CH_3O—⟨ NO_2 ⟩—NH_2 **A-51** → CH_3O—⟨ NO_2 ⟩—Br **A-73** → CH_3O—⟨ NO_2 ⟩—N-Tos ; CH_3-$CH(CH_2)_3$-NEt_2 **A-70**

A-51 $\xrightarrow{\times \ A-19}$ CH_3O—⟨ NO_2 ⟩—N=$C(CH_2)_3$-NEt_2 ; CH_3 **A-72**

**A-73** $\xrightarrow{A-67}$ **A-68** → **A-59** ⟶ **A-60**

The initial approach to the synthesis of the dimethoxylated target compound A-79 was abandoned for the same reason as that of the monomethoxy analog A-60, i.e., the instability of the 4-chloro-N,N-diethylpentylamine (A-64). The nitrated amino derivative A-77 is a key intermediate for the preparation of A-79. Accordingly, 4-bromo-5-nitroveratrole (A-81) was prepared by nitration of A-80. Treatment of A-81 with novoldiamine (A-19) is in progress. Meanwhile, it was also found that 4,5-dinitroveratrole (A-83) condensed with A-19 at 115° without solvent to give the desired intermediate A-77 in 62% crude yield as a dark orange syrup. The latter was purified by column chromatography. Several attempts were made to prepare a crystalline salt of A-77 but were unsuccessful. Compound A-77, however, was successfully reduced to A-78. Cyclization of A-78 with formic acid is being actively studied.

Reaction scheme with intermediates:

A-74 → A-75 → (A-64) → A-76

A-74: CH_3O–, CH_3O– substituted benzene with NH–SO_2–phenyl–CH_3

A-75: CH_3O, CH_3O, NO_2 substituted benzene with NH–SO_2–phenyl–CH_3

A-76: CH_3O, CH_3O, NO_2 substituted benzene with N–SO_2–phenyl–CH_3 and CH_3–$CH(CH_2)_3$–$N(C_2H_5)_2$

A-80 → A-81 → (A-19) → A-77

A-80: CH_3O, CH_3O, Br benzene

A-81: CH_3O, CH_3O, NO_2, Br benzene

A-77: CH_3O, CH_3O, NO_2 benzene with NH–CH_3–$CH(CH_2)_3$–$N(C_2H_5)_2$

A-82 → (A-19) → A-77; A-82 → A-83

A-82: CH_3O, CH_3O, NO_2, NO_2 benzene

A-83: CH_3O, CH_3O benzene with NH_2, NH_2

A-78: CH_3O, CH_3O benzene with NH_2 and NH–CH_3–$CH(CH_2)_3$–$N(C_2H_5)_2$

A-77 → A-78

A-83 → A-84

A-84: CH_3O, CH_3O benzimidazole ($1H$)

A-85: CH_3–$CH(Br)(CH_2)_3$–$N(CO$–$CH_3)$–C_2H_5

A-84 → (A-85) → A-86

A-86: CH_3O, CH_3O benzimidazole with CH_3–$CH(CH_2)_3$–N–C_2H_5, CO–CH_3

A-87: CH_3–$CH(Br)(CH_2)_3$– phthalimide

A-84 → A-88

A-88: CH_3O, CH_3O benzimidazole with CH_3–$CH(CH_2)_3$– phthalimide

A-79: CH_3O, CH_3O benzimidazole with CH_3–$CH(CH_2)_3$–$N(C_2H_5)_2$

A-88 → A-79; A-78 → A-79

13

An alternative approach has also been investigated. This involves alkylation of 5,6-dimethoxybenzimidazole(A-84). The required o-phenylene-diamine A-83 was obtained in good yield by catalytic reduction of A-82; sub-sequent cyclization gave a low yield of A-84. To avoid the use of the un-stable aminochloro compound A-64 as the alkylating agent, two other agents have been considered. The bromophthalimide A-87 was prepared and will be used for the preparation of A-88. Removal of the phthalimide group from the resulting compound followed by acylation and reduction should yield A-79. One attempt to prepare the other alkylating agent A-85 by treatment of the sodio salt of ethyl acetamide with 1,4-dibromopentane in refluxing toluene was without success. Apparently dehydrohalogenation took place in the basic medium and only ethyl acetamide was recovered.

B. α,β-Unsaturated Amino Acids and Related Compounds

N-Acetyldehydroleucine (B-4) was prepared according to a literature method.[21] The intermediate N-chloroacetyl-D,L-leucine[22] (B-2) was prepared from D,L-leucine (B-1) and chloroacetyl chloride. Compound B-2 was converted to the oxazolone B-3 by heating with acetic anhydride. Hydrolysis of B-3 yielded N-acetyldehydroleucine (B-4).
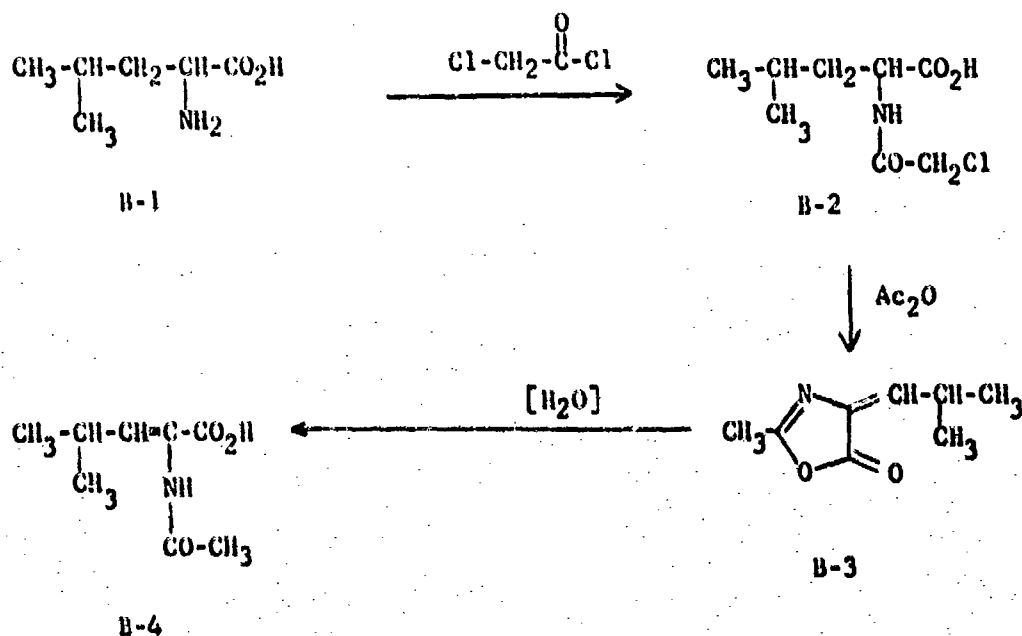

For the synthesis of 2-(p-chlorobenzamido)crotonic acid (B-8), a general Schotten-Baumann condition[23] was followed to prepare the intermediate B-6. Treatment of the latter with benzoyl chloride in pyridine[24] yielded the oxazolone B-7 which, upon hydrolysis with base, afforded the desired N-substituted aminocrotonic acid B-8.

B-5

B-6

B-7

$CH_3-CH=C-CO_2H$

B-8

C. Compounds Related to the Antimalarial Antibiotic Furanomycin

For the synthesis of a sulfur analog (C-5) of furanomycin, it is necessary to prepare the aldehyde C-3. Attempts to prepare C-3 directly by the reduction of the corresponding ester C-1a were not realized. It was then decided to prepare C-3 via the intermediate alcohol C-2. Reduction of C-1a with RED-AL gave a low yield of C-2. The reduction will be repeated by use of lithium aluminum hydride or diborane on either the ester C-1a or the acid C-1b. An attempt to oxidize C-2 to the aldehyde C-3 with selenium dioxide on graphite has, thus far, been unsuccessful.

C-1a. R C$_2$H$_5$
   b. R=H

C-2

C-3

C-5

C-4

Two other target compounds, 2-amino-2-(3-methyl-2-furyl)acetic acid (C-14) and 2-(3-methyl-2-tetrahydrofuryl)acetic acid (C-15), were prepared as follows: Darzen's glycidic ester condensation of 4,4-dimethoxy-2-butonone (C-6) and methyl chloroacetate (C-7) in the presence of sodium hydride, and subsequent thermal rearrangement of the condensation product C-8, yielded methyl 3-methyl-2-furoate[25] (C-9). This ester was hydrolyzed to the free acid C-10 and decarboxylated over copper in quinoline to give 3-methylfuran[26] (C-11). Vilsmeyer formylation of C-11 with phosphorus oxychloride, and dimethylformamide, according to Chadwick, et al.,[27] yielded a mixture of 3-methylfuran-2-carboxaldehyde (C-12) and 4-methylfuran-2-carboxaldehyde in a ratio of 30:4 (vpc). No effort was made to separate the 4-methyl isomer at this time. The formylated product was then converted to the corresponding hydantoin C-13, which, in turn, was hydrolyzed to the amino acid C-14 by the usual procedure.[28] Catalytic hydrogenation of C-14, yielded the corresponding tetrahydro compound C-15.
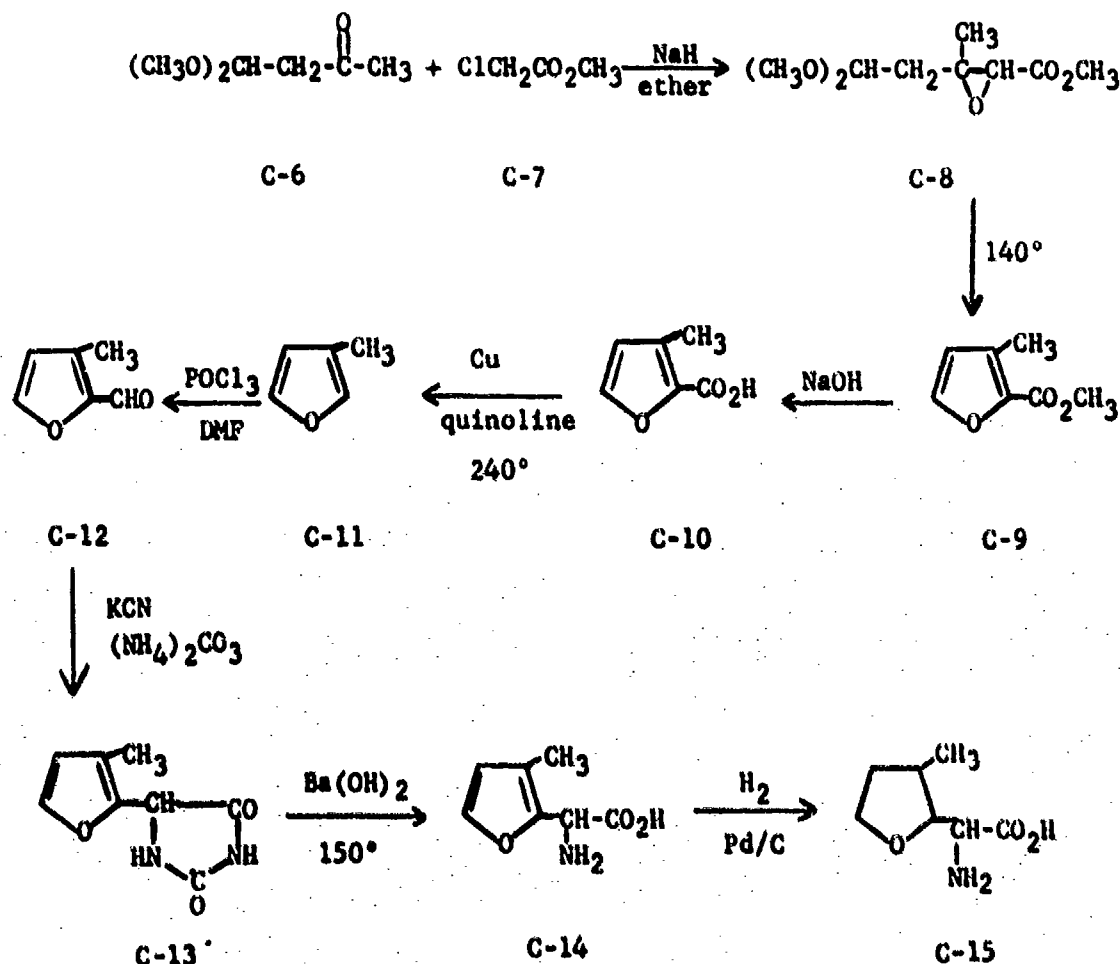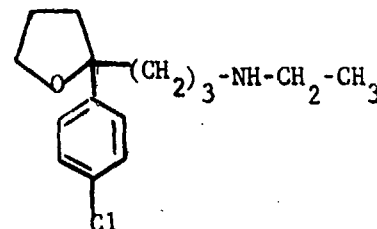
2-(p-Chlorophenyl)-2-cyanotetrahydrofuran (C-25), the intermediate needed for the preparation of the target compound C-16 and other target compounds C-17 and C-18, has been prepared.
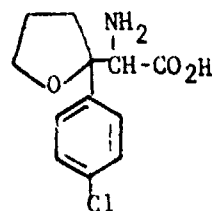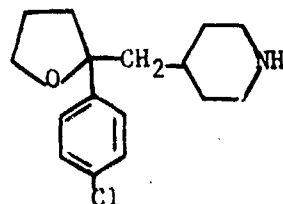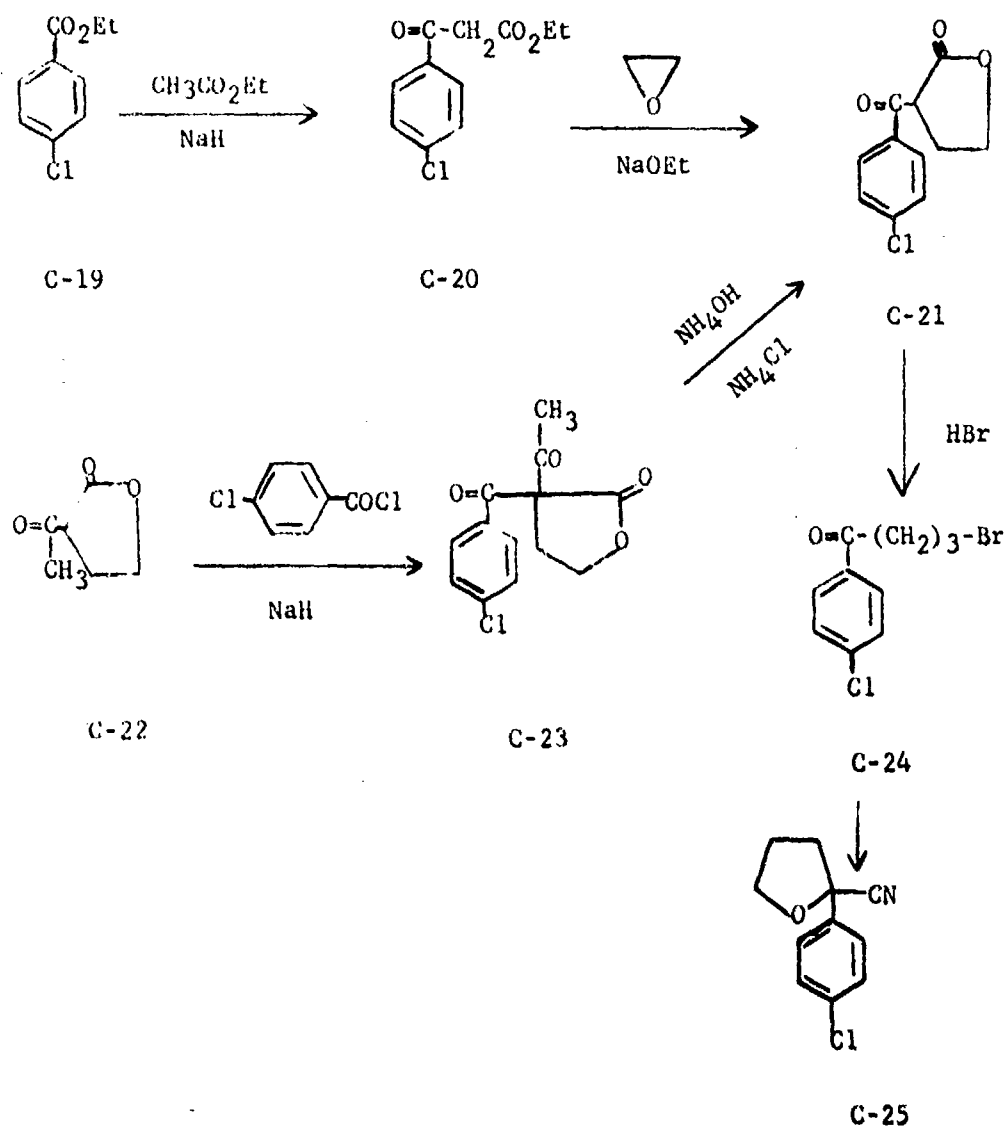

| | | |
| C-16 | C-17 | C-18 |

The benzoyllactone C-21, a precursor of 4-bromo-4'-chlorobutyrophenone (C-24), was initially prepared by condensation of ethyl p-chlorobenzoate (C-19) with ethyl acetate in the presence of sodium hydride[29] followed by treatment with ethylene oxide.[30] Since the yield of C-21 was low and the procedure was rather tedious, a different method, one involving acylation of α-acetyl-γ-butyrolactone[31] (C-22), was then used. The sodium salt of C-22 was treated wtth p-chlorobenzoyl chloride, α-acetyl-γ-(p-chlorobenzoyl)-γ-butyrolactone (C-23) was readily obtained, which could be deacetylated to the benzoyllactone C-21 on treatment with ammonium chloride in aqueous ammonia. Later, it was found that, for the preparation of C-21, it is more convenient to use the magnesium salt rather than the sodium salt of C-22 in the acylation reaction. In this manner, the desired benzoyllactone C-21 was obtained in satisfactory yield in a single step.

On heating with hydrobromic acid, the benzoyllactone C-21 was readily converted into 4-bromo-4'-chlorobutyrophenone (C-24), which, on

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C-19 → (CH3CO2Et, NaH) → C-20 → (epoxide, NaOEt) → C-21

C-22 → (Cl-C6H4-COCl, NaH) → C-23

C-21 → (NH4OH, NH4Cl) and (HBr) → C-24 → C-25

treatment with cuprous cyanide in boiling benzene, according to the pro-
cedure of Leroux,[12/] yielded the tetrahydrofuran derivative C-25. This prod-
uct was a clear liquid when first distilled, but gradually turned yellow.
Efforts to purify this compound by repeated distillation were not quite
successful, as no correct elemental analysis could be obtained. Neverthe-
less, on catalytic reduction in the presence of Raney nickel and semicar-
bazide,[33/] the nitrile compound C-25 was smoothly converted into a semi-
carbazone of the corresponding aldehyde C-26, which was characterized. An
effort to prepare the hydantoin C-27 from C-26 by the conventional method
was conducted, but so far no solid product could be obtained. Hydrolysis of
the crude product C-27 to the target compound C-16 is being studied.

18

C-21   C-26

C-16

C-27
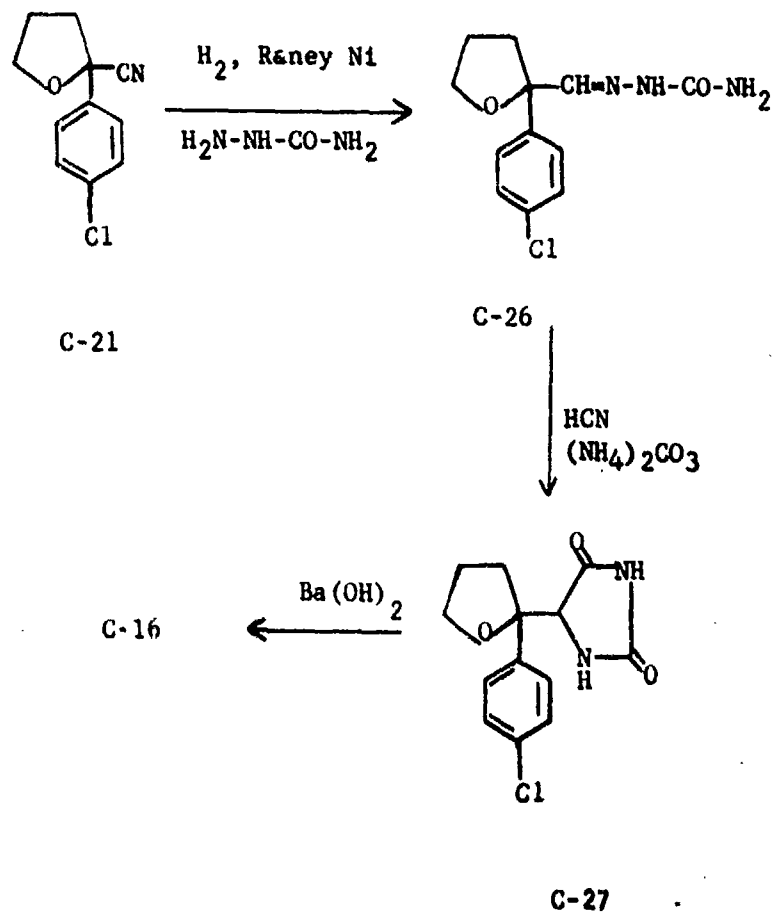
D. 3-Deazafebrifugine and Related Compounds

Synthesis of 3-deazafebrifugine[34/] (D-1) was initiated during this report period.

D-1
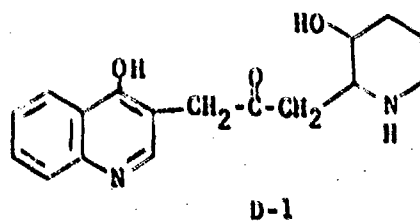
Our first synthetic approach to D-1 involves the addition of a quinoline-containing lithio compound D-2 to the carbonyl function of the piperidinyl derivative D-3 (or D-6). The resulting intermediate D-4 should be readily converted to D-1 through oxidation and cleavage of the two ether functions, illustrated as follows:
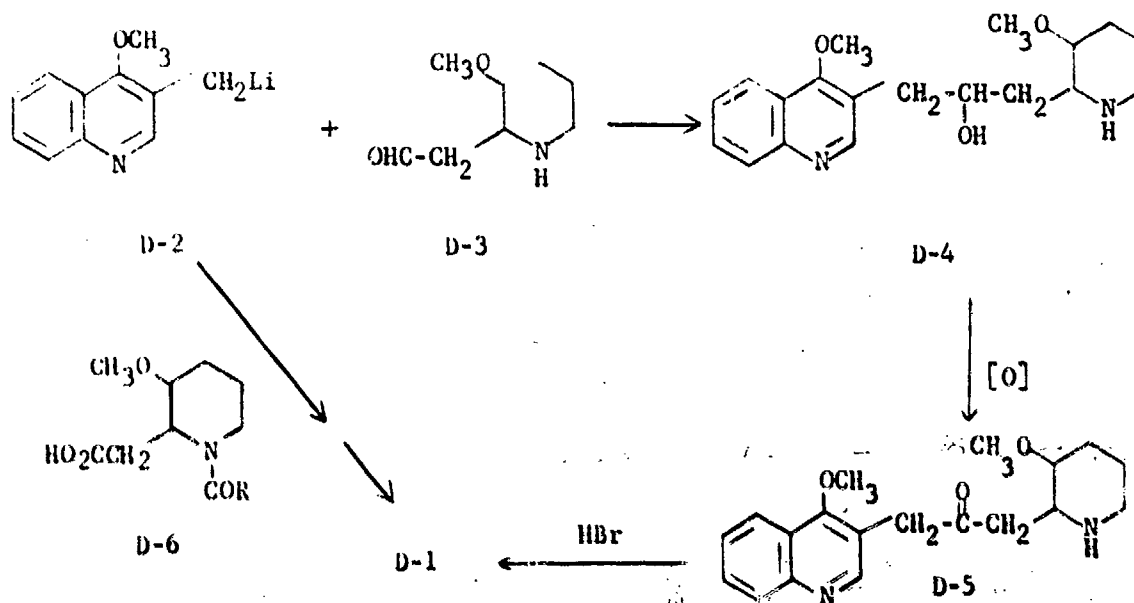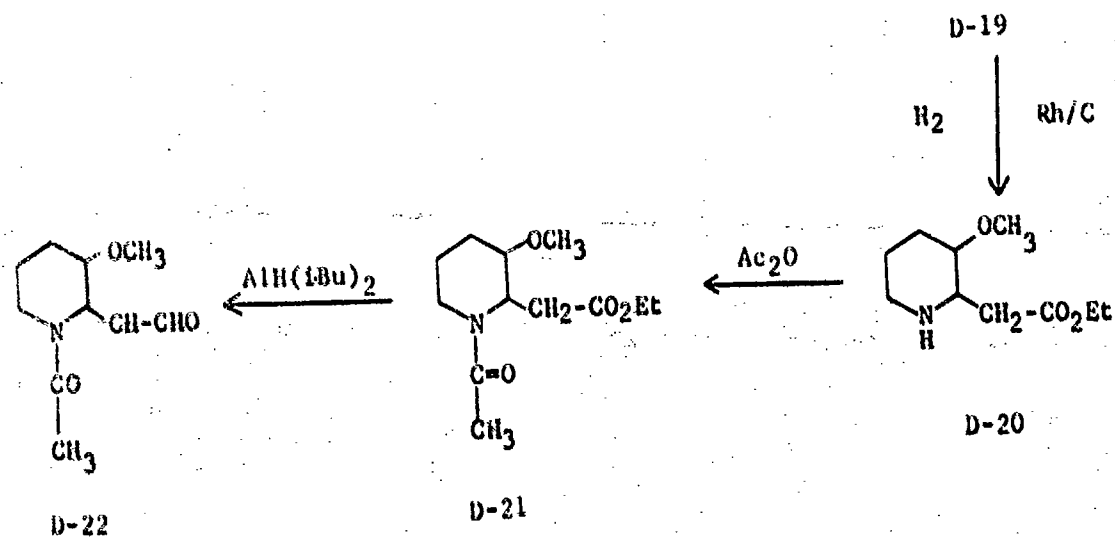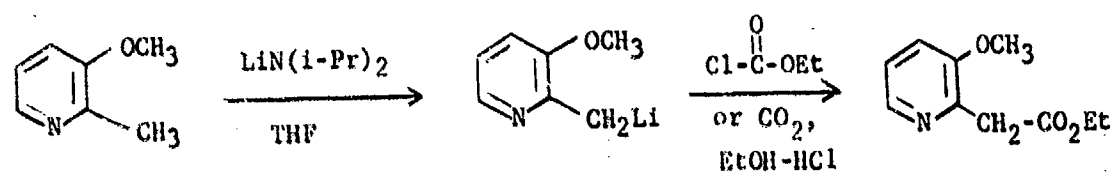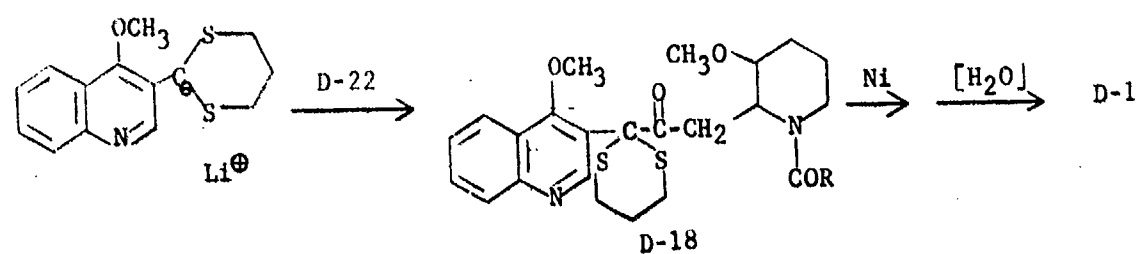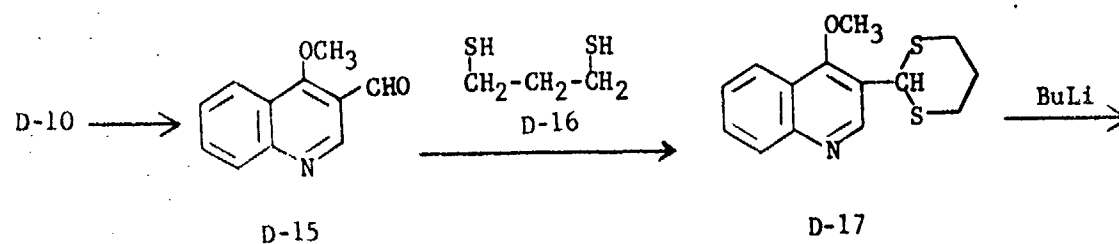

3-Hydroxymethyl-4-methoxyquinoline (D-11), the intermediate required for the preparation of the lithio compound D-2, was synthesized from aniline and diethyl ethoxymethylenemalonate, as shown in the following scheme.

D-10 →(Red-Al) D-11

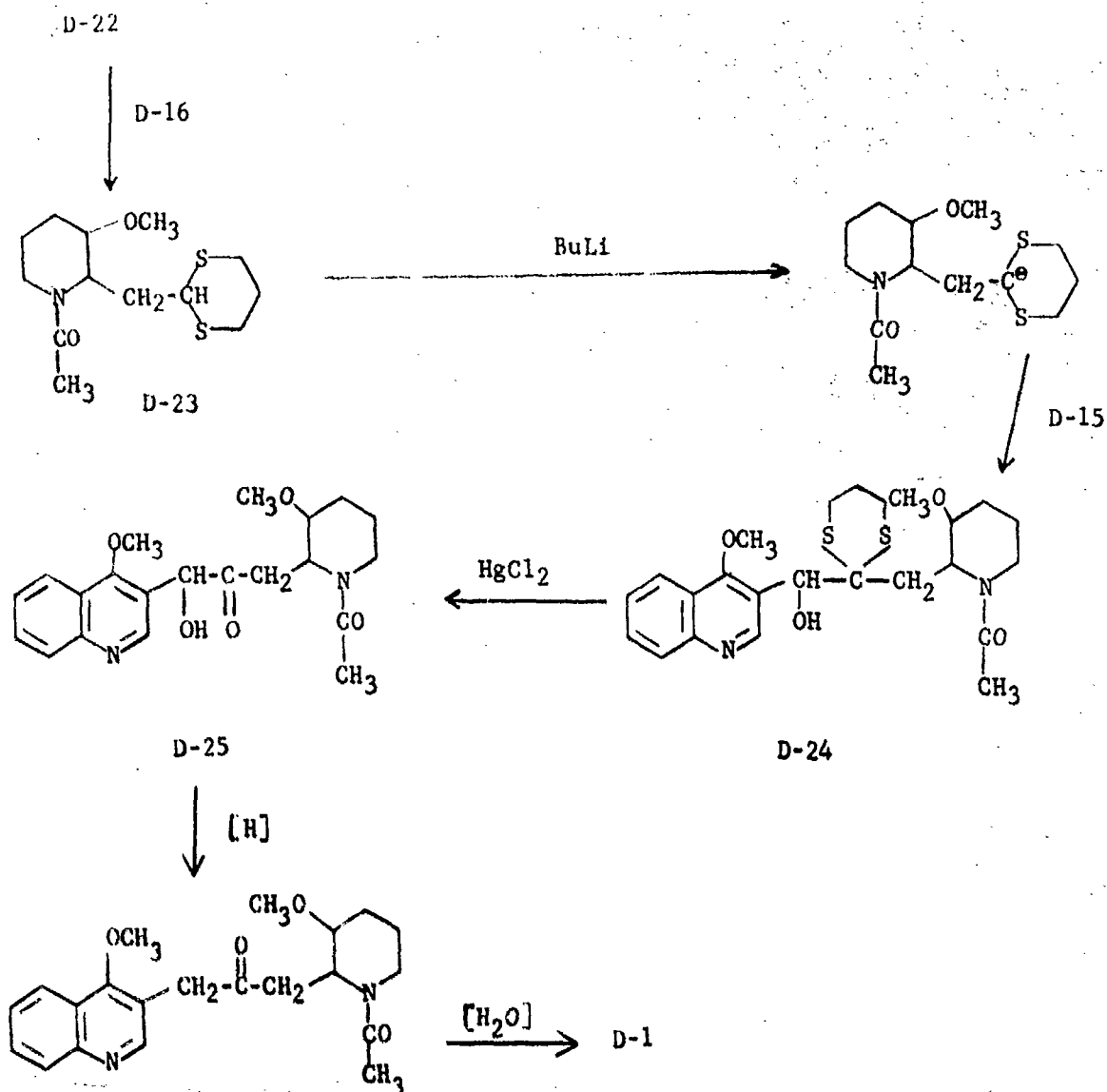D-11 → D-12

D-11 → D-13

D-14 → D-13
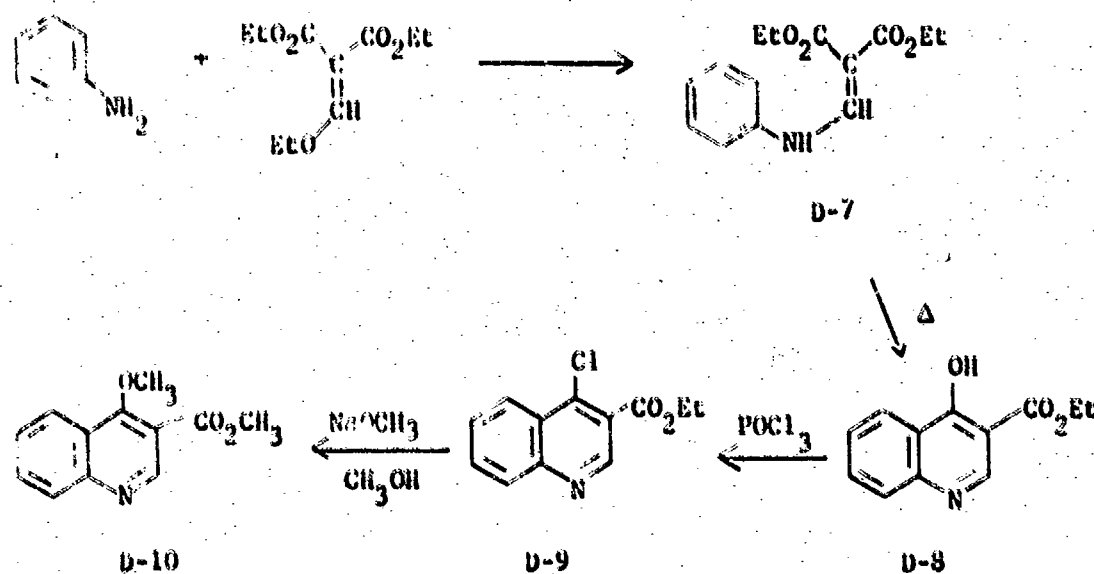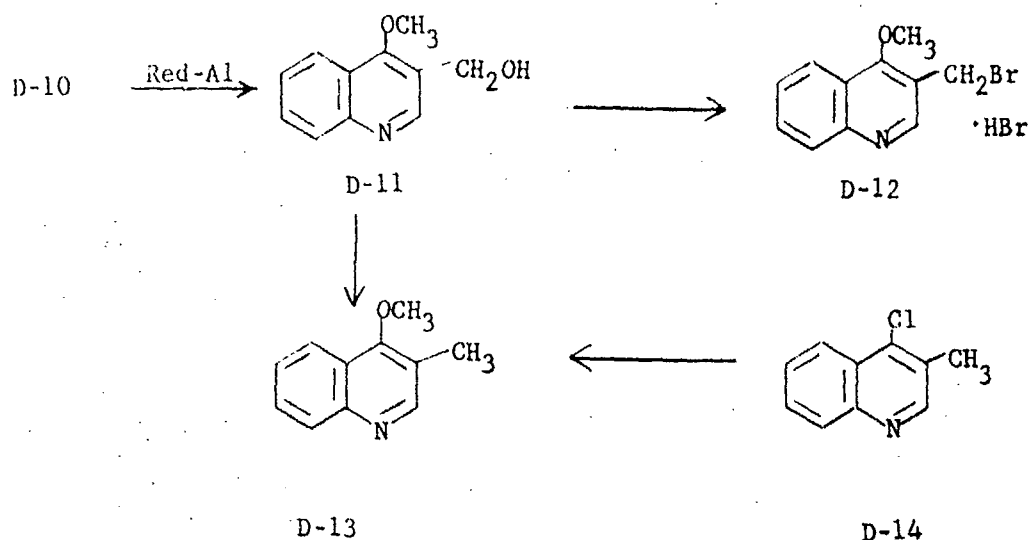
Since the desired hydroxymethyl compound D-11 could only be isolated
by column chromatography in small quantity by Red-Al reduction of the ester
D-10, a more practical preparative method was therefore sought. We have
attempted to improve the reaction conditions of this reduction but had little
success. Invariably a mixture of products resulted, and the desired product
was difficult to isolate. This difficulty is apparently due to simultaneous
reduction of the quinoline ring by the reducing agent. On the other hand,
lithium aluminum hydride is not so reactive toward this ester group, as the
reduction was found to be very slow in ether solution. In refluxing THF
solution the ester group was only slightly reduced after 1 day. Because of
this unexpected problem, this route is not being explored further.

In a modified first approach, which is shown in the following two
schemes, we tried to prepare the aldehyde D-15 by reduction of the ester D-10
with diisobutylaluminum hydride at -60° or -30°, or with Red-Al at -55°.
This reaction also did not succeed and only the starting ester was recovered.
Apparently the 3-quinolinecarboxyl group is comparatively unreactive toward
these reducing agents at low temperature. At higher temperatures these
reagents would obviously attack the quinoline ring,[36] leading to the forma-
tion of a mixture of products.

D-10 ⟶ [structure: 4-methoxyquinoline-3-carbaldehyde, OCH₃, CHO]
D-15

$\xrightarrow[\substack{CH_2-CH_2-CH_2 \\ \text{D-16}}]{\substack{SH \qquad SH}}$

[structure: dithiane-substituted quinoline, OCH₃]
D-17

$\xrightarrow{\text{BuLi}}$

[structure: dithianyl quinoline anion, OCH₃, $Li^{\oplus}$]

$\xrightarrow{\text{D-22}}$

[structure D-18: OCH₃ quinoline with dithiane, $C-\overset{O}{C}-CH_2$ linked to piperidine, CH_3O, COR]
D-18

$\xrightarrow{\text{Ni}}$ $\xrightarrow{[H_2O]}$ **D-1**

[structure: 3-methoxy-2-methylpyridine, OCH₃, CH₃]

$\xrightarrow[\text{THF}]{\text{LiN(i-Pr)}_2}$

[structure: OCH₃, CH₂Li pyridine]

$\xrightarrow[\substack{\text{or } CO_2, \\ \text{EtOH-HCl}}]{Cl-\overset{\overset{O}{\|}}{C}-OEt}$

[structure: OCH₃, CH_2-CO_2Et pyridine]
D-19

$\xdownarrow{\substack{H_2 \qquad Rh/C}}$

[structure D-20: piperidine, OCH₃, CH_2-CO_2Et, NH]
D-20

$\xleftarrow{\text{Ac}_2O}$

[structure D-21: piperidine, OCH₃, CH_2-CO_2Et, N–C=O–CH₃]
D-21

$\xleftarrow{\text{AlH(iBu)}_2}$

[structure D-22: piperidine, OCH₃, CH–CHO, N–CO–CH₃]
D-22

D-22

D-16 ↓

D-23

BuLi →

D-15 ↓

D-24

HgCl₂ ←

D-25

[H] ↓

[H₂O] → D-1

The second approach we have explored is centered on the proposed addition of the carbanion generated from the quinolineacetate D-29 to the piperidineacetate D-31 followed by hydrolysis and decarboxylation. Ethyl 4-hydroxy-3-quinolineacetate (D-27) was prepared in low yield by thermal cyclization of the intermediate D-26, which was readily obtained from aniline and ethyl formylsuccinate.

23
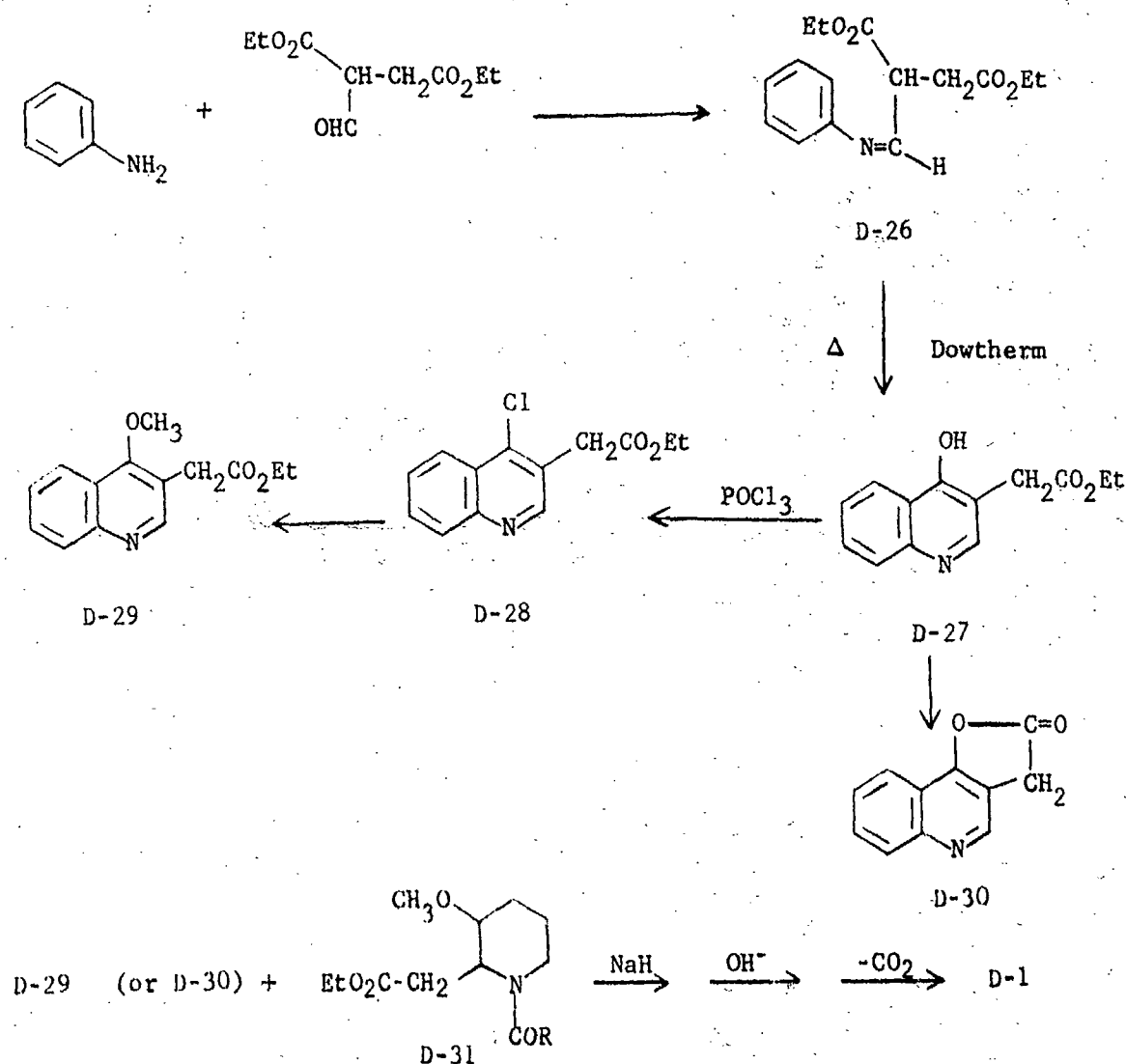
Conversion of the 4-hydroxy function of the compound D-27 to the corresponding chloro compound B-21 was readily carried out by the action of phosphorous oxychloride, and the structure of the product was substantiated by nmr. However, on treatment with excess sodium methoxide in methanol solution, the chloro compound D-28 did not yield the desired methoxy compound D-29. In fact, very little neutral product could be isolated by ether extraction. After being acidified to pH 5-6, there was formed a little solid product which showed only weak carbonyl absorption in ir. Similar results were obtained in several other experiments, including one using cuprous iodide as catalyst and at higher temperature. On the other hand, the 4-chloro compound D-28 appeared to be quite stable to methanolysis in the absence of sodium methoxide, even at temperatures up to 140°.

We have tried to condense a dianion D-32, which was formed by the action of two equivalents of lithium diisopropylamide on the hydroxyester D-27, with the piperidineacetate D-21, but the reaction did not appear to have taken place. When compound D-27 was added to a THF solution of two

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equivalents of lithioisopropylamide, a white precipitate was formed. When
this was heated with one equivalent of D-21 at 40-45° for 3.5 hr, the reac-
tion mixture still remained cloudy and, after it was worked up, only the
starting quinoline D-27 was recovered. The insolubility of the dilithio
compound D-32 in THF may presumably be responsible for the failure. It is
therefore obvious that the 4-hydroxyl function of D-27 should be protected
prior to this condensation reaction.

D-32
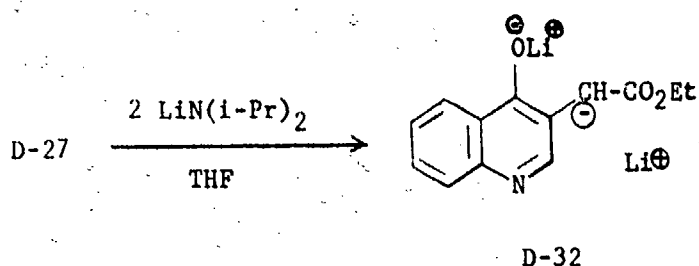
Attempted direct methylation of the 4-hydroxy group of compound
D-27 was carried out in DMF with methyl iodide and potassium carbonate,
in aqueous methanol with the same reagents, and in chloroform with diazo-
methane. These reactions all failed to give the desired methyl ether D-29.
Protection of the hydroxy function as tetrahydropyranyl ether or by trimethyl-
silyl group was also studied. These derivatives could not be formed under
normal reaction conditions, probably due to tautomerism of the 4-hydroxy-
quinoline system.

Subsequently, attempts were made to convert the hydroxyester D-27
to the lactone D-30. These experiments were also unsuccessful. The reaction
conditions and results are summarized below:

(1) Boiling D-27 in methanolic hydrochloric acid for 1 day
resulted in the formation of methyl ester (ester exchange).

(2) Boiling D-27 in methanolic aqueous potassium hydroxide for
1 day followed by addition of dilute hydrochloric acid. The mixture was
boiled again for 8 hr with the same result as above.

(3) Boiling D-27 in concentrated hydrochloric acid for 1 day
results in the formation of a little high melting solid ($> 250°$) with much
weaker carbonyl absorption in ir.

(4) Boiling D-27 in 50% sulfuric acid for 2 days: similar result.
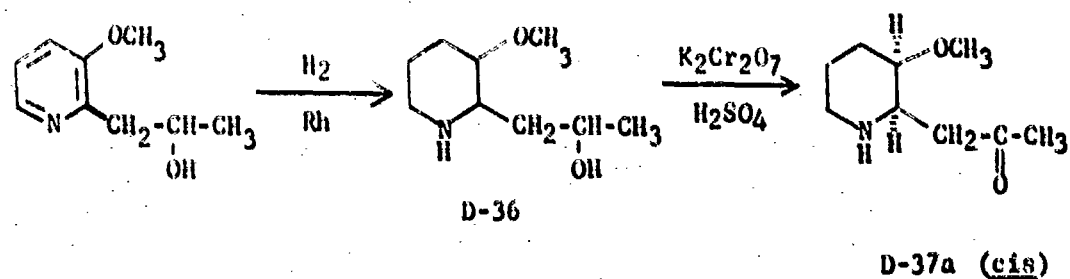
(5) Treatment of D-27 with sodium hydride in DMF at room tempera-
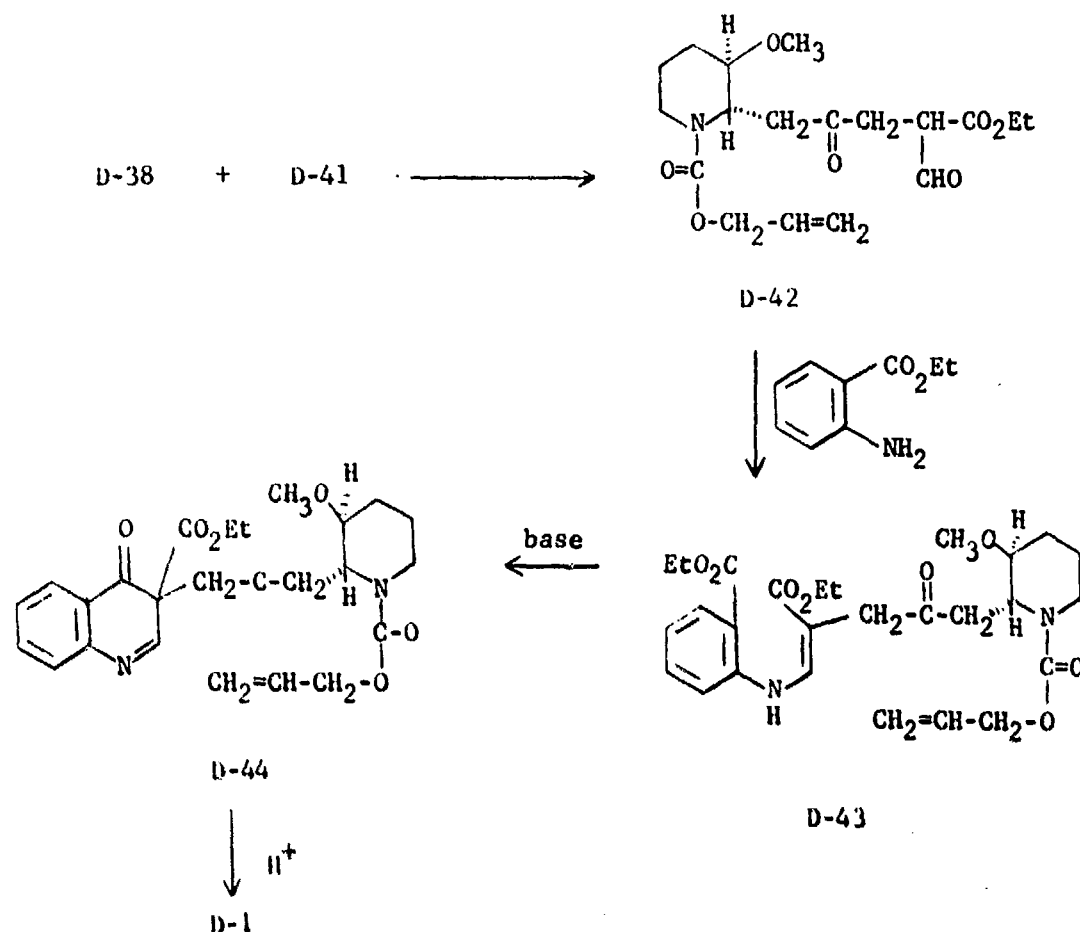ture for 3 days: no product could be isolated at pH 5.

A third approach involves construction of the entire side chain
portion prior to the cyclization of the quinoline ring. As early as 1946,

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it was shown that 3-alkyl-4-quinolinols could be prepared by alkylation of anilinocrotonates followed by thermal cyclization.[38,39] For example, endochin (D-35) was obtained in good overall yield by alkylation of ethyl β-(3-methoxyanilino)crotonate (D-33) with heptyl iodide and subsequent thermal cyclization of the alkylated product D-34.


D-33

$CH_3-(CH_2)_6-I$

Na, xylene

D-34

250°

D-35
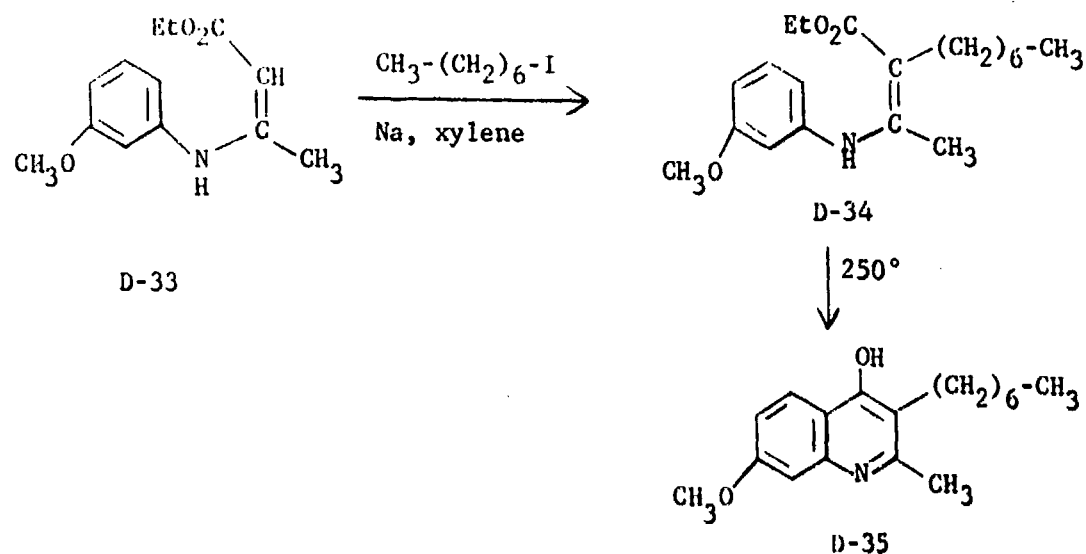
Using endochin as a model, experiments depicted by the following scheme were studied. The necessary intermediates D-38[40] and D-39[41] were prepared according to the literature methods. Isomerization of the cis-isomer to the trans-isomer was carried out at the ketone stage.[42] Compound D-38, which contains an α-bromoketone, would be a good alkylating agent.

H_2
Rh

D-36

$K_2Cr_2O_7$
H_2SO_4

D-37a (cis)

When alkylation of D-39 was carried out with the sodio salt of compound D-38 in toluene at 50-60° for 6 hr and at room temperature for 2 days, a small amount of an oily product was obtained. Based on its nmr spectrum, the oily substance was not the desired product D-40. When the reaction was carried out under more drastic reaction conditions, such as heating the mixture at 100-110° for 1 hr, the reaction mixture darkened and a number of products (tlc) were formed.

Since compound D-38 turned dark red at 0° in a few days, it was believed that the aforementioned reaction conditions may be too severe and a lower reaction temperature might be useful. Accordingly, the following alkylation reaction was attempted.

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D-38 + D-41 ⟶ D-42

D-43

D-44

D-1

Ethyl sodioformylacetate[41] (D-41) was prepared in situ by
stirring equivalent amounts of ethyl acetate, ethyl formate, and sodium
dispersion in ether at room temperature for 2 days under nitrogen. An
equivalent amount of D-38 was then added and refluxed for 11 hr, followed
by addition of an equivalent amount of ethyl anthranilate. The mixture,
after being refluxed for an additional 10 hr, still contained mostly the
starting ethyl anthranilate and only a small amount (< 5%) of an aromatic
compound was formed, as detected by tlc (silica gel with fluorescent indicator).
Addition of acetic acid to the mixture and refluxing for 2 hr did not change
the characteristics of the reaction mixture. The small amount of aromatic
compound was, therefore, not isolated and identified.

A modified third approach we have recently initiated to study is
depicted in the following scheme. We have already prepared 100 g of
3-methoxy-2-methylpyridine. The diethyl acetal of 3-cyanopropanal, the pre-
cursor of the other starting material, is commercially available. The
pivotal step in this route will be the base catalyzed cyclization of D-45
to the dihydroquinoline system D-46.
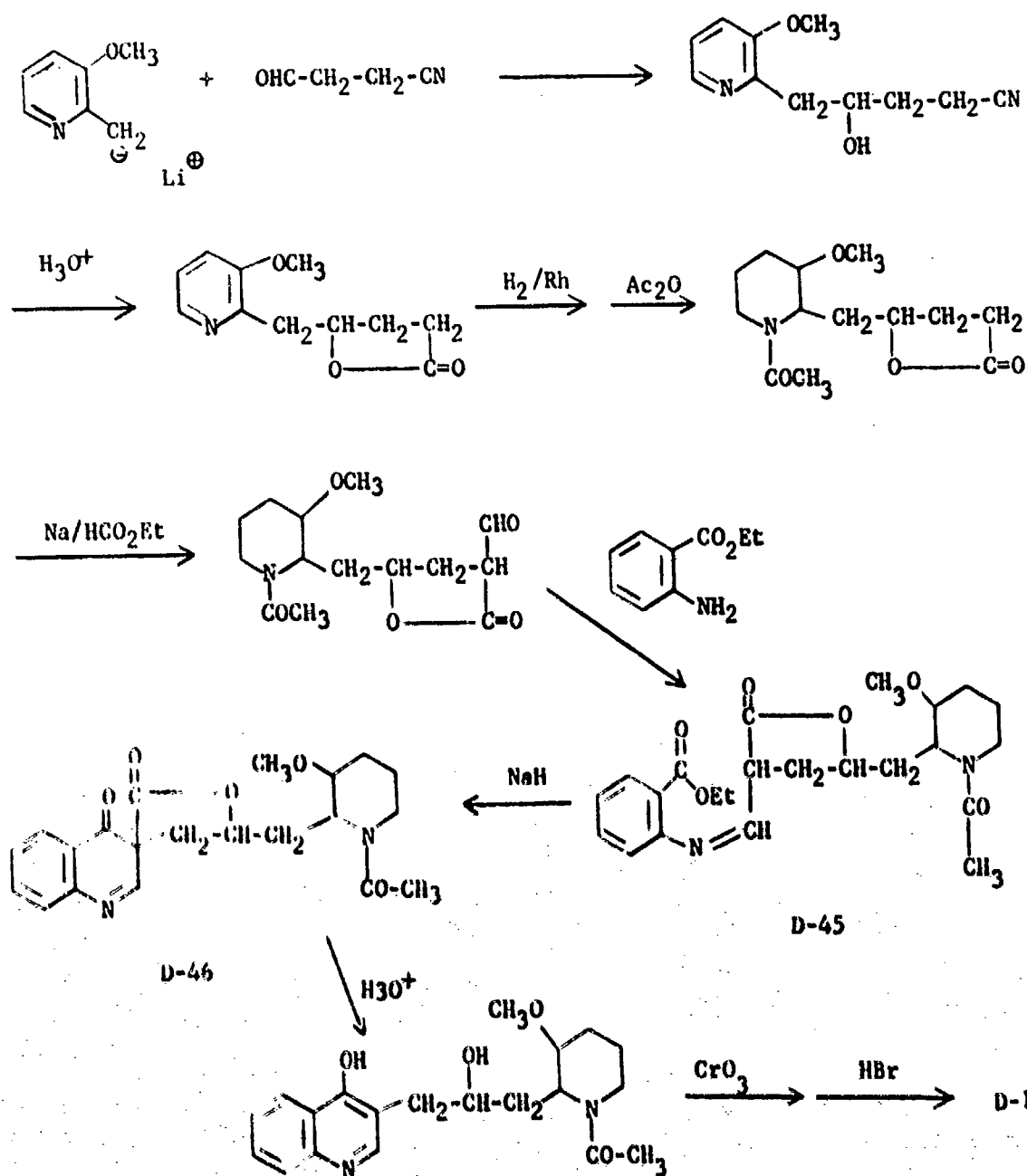
III. EXPERIMENTAL

N^1, N^1-Diethyl-N^4-(3,4-dimethoxyphenyl)-1,4-pentanediamine   (A-3)

A mixture of 16.7 g (0.1 mole) of 4-nitroveratrole (A-1), 18.8 g (0.12 mole) of 5-diethylamino-2-pentanone (A-2), 100 mg of platinum oxide, 10 ml of acetic acid and 175 ml of absolute ethanol was hydrogenated at 60 psig for 72 hr. The resulting mixture was filtered and the filtrate evaporated in vacuo to a dark oil. This was distilled to give 22 g (72% yield) of a light red liquid, b.p. 147-152°/0.05 mm; ir: 3400 cm^{-1} (NH); tlc: Rf 0.54 (Al_2O_3-acetone).

Anal. Calcd. for $C_{17}H_{30}N_2O_2$: C, 69.34; H, 10.27; N, 9.52.
Found: C, 69.46; H, 10.51; N, 9.68.

4-Bromoveratrole (A-5)

A literature method[3] was followed. A mixture of 207 g (1.5 mole) of veratrole, 267 g (1.5 mole) of N-bromosuccinimide, and 240 ml of CCl_4 was placed in a round bottom flask equipped with a reflux condenser protected by a $CaCl_2$ drying tube. The mixture was refluxed on a steam bath for 6 hr, then allowed to stand overnight at room temperature. The insoluble succinimide was separated from the dark red solution by filtration and washed with CCl_4 (3 x 60 ml). The combined filtrate and washings were evaporated and the residual liquid fractionally distilled in vacuo to give 271 g (84% yield) of 4-bromoveratrole (A-5) as a pale yellow oil, b.p. 102-109°/2 mm. (lit,[3] b.p. 117-119.5°/5 mm).

4-Bromo-5-nitroveratrole (A-6)

A literature method[4] was followed. To 75 ml of concentrated HNO_3 at 10° was added, with stirring, 21.7 g (0.1 mole) of A-5 during 20 min. The temperature rose to 40°. Stirring was continued at room temperature for 30 min. The solution was poured into 100 ml of ice water and the resulting mixture stirred for 30 min. The precipitated product was collected by filtration to give 17.2 g (66% yield) of A-6, m.p. 106-110°. Three recrystallizations gave an analytical sample, m.p. 120-121° (lit,[4] m.p. 122-124°).

Anal. Calcd for $C_8H_8BrO_4$: C, 36.67; H, 3.05; N, 5.34. Found: C, 36.89; H, 3.32; N, 5.26.

4-Bromo-5-[(5-diethylamino-2-pentyl)amino]veratrole   (A-9)

A mixture of 10.5 g (0.04 mole) of A-6 and 5% Pt/C in 150 ml of benzene was hydrogenated at 30 psig. The hydrogenation was completed in 70 min. Catalyst was removed by filtration, and the filtrate was evaporated under reduced pressure to yield crude A-7 as a light brown liquid, the ir of which had a characteristic NH_2 absorption at 3450 and 3350 cm^{-1}. The crude A-7 was mixed with 8.8 g (0.044 mole) of 5-diethylamino-2,2-dimethoxypentane and 0.2 g of p-toluenesulfonic acid monohydrate, and was heated with stirring at 160-165° for 2 hr. After cooling, the reaction mixture was diluted with 180 ml of Et_2O, washed with 30 ml of 5% Na_2CO_3 and 30 ml of saturated aqueous NaCl, then dried (K_2CO_3). Removal of Et_2O afforded crude A-8 as a light brown liquid, ir (neat) 1660 cm^{-1} (C=N).

The crude A-8 was dissolved in 100 ml of absolute EtOH and cooled to 0-5° in an ice water bath. To the solution was added, in several portions, 5 g of $NaBH_4$. The resulting mixture was stirred at room temperature overnight. It was diluted with 400 ml of H_2O, extracted with Et_2O (3 x 100 ml) and dried ($MgSO_4$). Evaporation of the solvent yielded 12 g of crude A-9 as a liquid. Kügelrohr distillation at 80-85°/0.3 mm removed the lower-boiling component from the product and analytically pure A-9, 9.6 g, was collected at 125-130°/0.3 mm. The overall yield of A-9 from A-6 was 65%.

Compound A-9 had the following characteristics; ir (neat): 3400 cm^{-1} (NH); uv: λ_{Max}^{EtOH} 247 (ϵ 14,200) and 312 nm (ϵ 5,600); nmr ($CDCl_3$): δ 0.96 (6H, t, J = 6 cps, two terminal CH_3 of the diethyl group), 1.18 (3H, d, J = 6 cps, CH_3 attached to the C-1 of butyl group), 1.36-1.70 (4H, m, protons at C-2 and C-3 of the butyl group), 2.20-2.64 (6H, m, three CH_2 protons attached to the tertiary N), a broad peak at 3.40 (1H, methine proton at C-1 of the butyl group) 3.68 and 3.74 (6H, s, two OCH_3), 6.22 and 6.88 (2H, s, two aromatic protons).

Anal. Calcd for $C_{17}H_{29}BrN_2O_2$: C, 54.72; H, 7.77; N, 7.51. Found: C, 55.00; H, 7.95; N, 7.47.

2-Bromo-4,5-methylenedioxy-N-(5-diethylamino-2-pentyl)aniline (A-13)

A solution of 9 g (0.038 mole) of 2-bromo-4,5-methylenedioxynitro-benzene (A-10) in 150 ml of benzene was hydrogenated under 44 psig in a Parr hydrogenator in the presence of 5% platinum-on-charcoal. A theoretical amount of H_2 was absorbed after 4 hr. The catalyst was removed by filtration and benzene was distilled from the filtrate under N_2. The residual crude 2-bromo-4,5-methylenedioxyaniline (A-11) [its ir spectrum had the NH absorption at 3400 and 3300 cm^{-1}] was mixed with 8 g of 2,2-dimethoxy-5-diethylaminopentane and 0.2 g of p-toluenesulfonic acid monohydrate and heated with stirring at 160-165° for 2 hr. Methanol, one of the reaction products, was removed by distillation during the heating. After being cooled, the reaction mixture was diluted with 200 ml of Et_2O. The solution was washed with 5% Na_2CO_3, then with saturated NaCl solution, and dried (K_2CO_3). Evaporation of the solvent yielded the anil A-12 as a light brown liquid. Its ir showed a medium absorption of C=N at 1660 cm^{-1}.

The crude anil A-12 was dissolved in 50 ml of absolute EtOH, followed by portionwise addition of 5 g of $NaBH_4$. The mixture was stirred overnight at room temperature and excess $NaBH_4$ was decomposed by addition of 300 ml of H_2O. The resulting aqueous solution was extracted with Et_2O (3 x 70 ml) and dried (K_2CO_3). Evaporation of solvent afforded a dark brown liquid. This was dissolved in 5 ml of $CHCl_3$ and column chromatographed over 100 g of silica gel (Woelm, Act. I) eluting initially with 900 ml of $CHCl_3$, then with 825 ml of $CHCl_3$-MeOH (9:1). The fraction from $CHCl_3$ eluent contained 1.5 g of a dark brown liquid, which was a mixture of A-13 and other impurities. The fraction from $CHCl_3$-MeOH contained 6.5 g of A-13. Molecular distillation of the latter at 110-115°/0.4 mm gave 5.5 g (40% overall yield) of analytically pure A-13. ir (neat): 3400 (NH), 2790 cm^{-1} (O-CH_2-O), nmr ($CDCl_3$): δ 0.96 (t, J = 6 cps, 6H, two CH_3 of the ethyl group), 1.15 (d, J = 6 cps, 3H, CH_3 of the 1-methylbutyl group), 1.25-1.70 (m, 4H, two CH_2 of C-1 and C-2 in the butyl group); 2.20-2.68 (m, 6H, three CH_2 around the terminal N atom), 3.12-3.50 (m, 1H, methine proton on C atom), 3.72 and 3.80 (1H, proton on N atom), 5.72 (s, 2H, O-CH_2-O), 6.23 and 6.80 (two s, 2H, aromatic H).

Anal. Calcd. for $C_{16}H_{25}BrN_2O_2$: C, 53.78; H, 7.05; N, 7.84. Found: C, 53.50; H, 7.17; N, 7.81.

5-Diethylamino-2-pentanol (A-14)

To a stirred solution of 83 ml (0.28 mole) of 70% RED-AL in benzene (Aldrich) and 250 ml of dry benzene under nitrogen was added, during 45 min, a solution of 78 g (0.5 mole) of 5-diethylamino-2-pentanone (A-2) in 150 ml of dry benzene. The mixture was stirred for 4 hr and the syrupy reaction mixture was slowly added, through a dropping funnel, to a stirred ice-cold solution of 130 ml of 20% sodium hydroxide. After 2 hr, the upper organic layer was separated and the lower aqueous layer extracted

with ether (2 x 50 ml). The organic layer and the ether extracts were combined, dried and evaporated. The residue was distilled in vacuo to give 65 g (81% yield) of A-14, b.p. 87-89°/6 mm (Lit,[6] b.p. 80°/3 mm).

4-Chloro-N,N-diethylpentylamine Hydrochloride (A-15)

To a stirred solution of 62.5 g (0.4 mole) of A-14 in 160 ml of chloroform at -10" was added dropwise, during 30 min, a solution of 30 ml (49 g; 0.41 mole) f thionyl chloride in 65 ml of chloroform. The mixture was allowed to warm to room temperature overnight. It was then evaporated in vacuo to a syrup (ca. 100 g). This was shaken vigorously with 250 ml of ethyl acetate. The resulting solid was collected by filtration and washed with cold ethyl acetate. There was obtained 55 g (64% yield) of crude A-15, m.p. 85-87°. Recrystallization from ethyl acetate yielded an analytically pure sample, m.p. 96-97° (Lit,[5] m.p. 98°).

6-Nitroquinoxaline (A-17)

The procedure of Jones and McLaughlin for the preparation of quinoxaline[7] was followed. Glyoxal-sodium bisulfite adduct was prepared by mixing 150 ml of 40% glyoxal (1.44 mole) (Aldrich) and 218 g (2.08 mole) of sodium bisulfite in 1,000 ml of hot (60") water and subsequent heating of the resulting solution at 60" for 30 min. The hot mixture, which contained the precipitated adduct, was added to a stirred suspension of 153 g (1 mole) of 4-nitro-o-phenylenediamine (A-16) and 2,000 ml of hot (70°) water. The resulting mixture was heated at 70° until all solids were dissolved (ca. 1 hr). After cooling to room temperature, 400 g of $Na_2CO_3 \cdot 2H_2O$ was added with stirring. The precipitated solids were collected by filtration and dried. It was dissolved in 5.5 liter of 95% ethanol and filtered white hot. The filtrate, on cooling, gave 62 g (35% yield) of 6-nitroquinoxaline, m.p. 177-179° (Lit,[8] m.p. 177°).

6-Aminoquinoxaline (A-18)

The method of Case and Brennan[9] was used. A mixture of 41 g (0.23 mole) of A-17, 161 g of $SnCl_2 \cdot 2H_2O$ and 700 ml of ethanol was refluxed for 5 hr. The resulting solution was concentrated to about 100 ml and decanted from the dark red precipitate. The ethanol solution was basified with 20% NaOH. The resulting precipitate was separated by filtration and the filtrate extracted with ether (4 x 200 ml) and dried ($MgSO_4$). Evaporation of ether yielded a brown solid, which was dissolved in 500 ml of benzene. The solution was concentrated in vacuo to 100 ml and chilled to

afford 14 g (41% yield) of 6-aminoquinoxaline (A-18) as a brown solid, m.p. 152-155° (Lit,[9] m.p. 157-158°).

5-Diethylamino-2,2-dimethoxypentane[10] (A-19)

Method 1

A stream of dry hydrogen chloride was passed through a solution of 62.8 g (0.4 mole) of 5-diethylaminopentan-2-one in 330 ml of CH_3OH until 14.5 g of HCl was absorbed. To the resulting solution was added 50.8 g (0.48 mole) of trimethyl orthoformate and the mixture was refluxed for 30 min. The reaction solution was poured into a beaker containing 800 ml of saturated Na_2CO_3 solution. The resulting basic solution was extracted with ether (4 x 200 ml), dried (K_2CO_3), and evaporated to give a dark red liquid. It was distilled to obtain 46.7 g (58% yield) of A-19 as a colorless liquid, b.p. 86-89°/3.1-4.0 mm (Lit,[10] b.p. 106°/8 mm).

Method 2

A better yield of A-19 could be obtained by the use of redistillated 5-diethylaminopentan-2-one. Thus, 79 g (0.5 mole) of the redistilled ketone in 400 ml of CH_3OH was saturated with dry hydrogen chloride until the solution absorbed 18 g of HCl. Trimethyl orthoformate (63.5 g, 0.6 mole) was then added and the mixture was refluxed for 30 min. After overnight standing, the reaction mixture was poured into 1,000 ml of saturated aqueous Na_2CO_3 solution and the resulting mixture extracted with Et_2O (3 x 400 ml). The Et_2O extract was dried (K_2CO_3) and evaporated. Distillation of the residue gave 96.4 g (98% yield) of 5-diethylamino-2,2-dimethoxypentane as a colorless liquid, b.p. 78-82°/2.5-3.2 mm.

6-[5-Diethylamino-2-pentyl)amino]quinoxaline (A-21)

A mixture of 10.9 g (0.075 mole) of 6-aminoquinoxaline (A-18) 20.8 g (0.09 mole) of 5-diethylamino-2,2-dimethoxypentane (A-19), and 100 mg of p-toluenesulfonic acid monohydrate was stirred and heated in an oil bath at 160° for 3 hr. Methanol was removed by distillation during the reaction. The resulting mixture was diluted with 305 ml of ether and washed successively with 50 ml each of 5% Na_2CO_3, water and saturated sodium chloride solution. After being dried over K_2CO_3, the ether solution was evaporated to yield a dark red residue; its ir (neat) had a strong C=N absorption band at 1660 cm^{-1}.

The dark red liquid, which contained the intermediate anil A-20, was subjected directly to sodium borohydride reduction without further purification. It was dissolved in 270 ml of absolute ethanol and stirred with 7.5 g of $NaBH_4$ at room temperature for 20 hr. The resulting solution was diluted with 500 ml of water and extracted with ether (3 x 150 ml). The combined ether solution was dried (K_2CO_3) and evaporated to give a viscous dark red liquid. Its ir spectrum (neat) had a strong NH absorption band at 3250 cm^{-1} and no C=N absorption at 1660 cm^{-1} was observed. The crude product was dissolved in 30 ml of chloroform and column chromatographed on 350 g of silica gel (Woelm, Act I), eluting with $CHCl_3$-MeOH (4:1). The eluant was monitored frequently during the chromatographic process by tlc (silica gel, $CHCl_3$-MeOH, 4:1). The first 280 ml-fraction contained both unreacted 6-aminoquinoxaline (A-18) and 5-diethylaminopentan--2-one. The next 200 ml-fraction (2.2 g after evaporation) contained mostly the desired product A-21 but was still contaiminated by a small amount of reactants A-18 and A-19. The third 2250 ml-fraction, (8.0 g after evaporation) contained mostly the desired product A-21 but was contaminated by a red material. The overall yield of A-21, up to this stage of purification, was 47%. The material obtained from the preceding third fraction was again column chromatographed using alumina (Woelm, neutral, Act I, 150 g) as the absorbent and chloroform as eluant. The fractions prior to the elution of a yellow band were discarded. The first 100 ml fraction of the yellow eluant contained 4.6 g of the product A-21 and the second 500 ml-fraction contained 3.0 g of A-21; the red material remained in the column. The recovery of the desired product from the previous chromatographic purification was 95%. The ir spectrum (neat) of A-21 had a strong NH absorption at 3250 cm^{-1}. The nmr spectrum ($CDCl_3$) had two doublets at δ 8.52 and 8.36 (J=2 cps, 2H, protons at C-2 and C-3). [Assignment of the aromatic protons is based on a comparison with 6-aminoquinoxaline,[43/] with the assumption that electron density distribution on the ring of both compounds is comparable]. One doublet at δ 7.70 (J_{7-8}=9 cps, 1H, proton at C-8), a quartet at 7.01 (J_{7-8}=9 cps, J_{5-7}=2.5 cps, 1H, proton at C-7), a doublet at 6.83 (J_{5-7}=2.5 cps, 1H, proton at C-5), a multiplet at 3.55 (1H, methine proton on the side chain), a multiplet at 2.56-2.22 (6H, three methylene protons attached to tertiary nitrogen on the side chain), a multiplet at 1.70-1.40 (4H, two methylene protons), a doublet at 1.22 (J=6 cps, 3H, CH_3), a triplet at 0.96 (J=7 cps, 6H, two CH_3 at the diethyl terminal), and twin peaks at 5.05 and 4.98 (1H, NH).

Distillation of the product obtained from the second fraction (3 g) using the Kugelröhr Distillation Apparatus at an over temperature of 125 ± 3° (0.1 mm) gave 2.0 g of analytically pure sample.

Attempts to prepare different salts failed to yield any solid product.

Anal. Calcd. for $C_{17}H_{26}N_4$: C, 71.32; H, 9.09; N, 19.58. Found: C, 71.03; H, 9.09; N, 19.51.

2-Methoxy-4,5-dinitroacetanilide (A-23)

To a suspension of 84 g (0.5 mole) of 2-methoxy-5-nitroaniline (A-22) (Aldrich) in 450 ml of AcOH at room temperature was added 150 ml of Ac_2O in one portion. The suspension became clear but soon a green solid precipitated whereupon the temperature of the reaction mixture spontaneously rose to 45°. The mixture was stirred for 30 min and cooled to room temperature with a cold water bath. To the mixture was added dropwise 50 ml of red fuming HNO_3 (d. 1.56) in 1 hr. The green solid redissolved toward the end of the addition. The resulting solution was stirred at room temperature for another 4 hr, then poured into 2500 ml of ice water. The aqueous layer was decanted and the remaining paste washed three times with ice water. To the paste was added 300 ml of MeOH. Trituration and pulverization of the paste yielded a yellow solid, which was collected and recrystallized from 700 ml of MeOH to afford 24 g (18% yield) of A-23 as yellow needles, m.p. 162-163° (lit,[11] m.p. 162-163°); ir (KBr): 3380, 1700 cm^{-1}. λ $_{Max}^{EtOH}$ 254 nm (ϵ 16,900).

Anal. Calcd for $C_9H_9N_3O_6$: C, 42.35; H, 3.53; N, 16.47. Found: C, 42.17; H, 3.58; N, 16.27.

6-Methoxy-7-acetamidoquinoxaline (A-25)

A mixture of 12.8 g (0.05 mole) of A-23 and 1 g of 10% Pd/C in 250 ml of MeOH was hydrogenated at 40 psig for 90 min. Catalyst was removed by filtration and the filtrate evaporated to give crude 2-methoxy-4,5-diaminoacetanilide (A-24) as an oily residue, which turned dark green on exposure to air.

The oil A-24 was dissolved in 120 ml of H_2O and stirred with 14 g (0.052 mole) of glyoxal disodium bisulfite at 70° for 2 hr. The resulting yellow solid was collected by filtration to give 5.4 g of the quinoxaline A-25. Addition of 20 g of Na_2CO_3 to the filtrate precipitated another 4.4 g of A-25. The filtrate resulting from the second filtration was extracted with CH_2Cl_2 (4 x 50 ml) to obtain still additional 0.4 g of the same product. The total yield of A-25 was therefore 10.4 g (96%), m.p. 200°. Three recrystallizations from 2-propanol yielded an analytical sample, m.p. 200°; ir: 3300 and 1670 cm^{-1} (N-acetyl carbonyl); λ $_{Max}^{EtOH}$ 251 (ϵ39,300), 356 nm (ϵ14,300); nmr (DMSO-d$_6$): δ 2.21 (3H, s, COCH$_3$), 4.01 (3H, s, OCH$_3$); 7.41 (1H, s, aromatic proton), 8.68 (2H, s, aromatic protons), 8.78 (1H, s, aromatic proton), 9.00 (1H, s, NH).

Anal. Calcd for $C_{11}H_{11}N_3O_2$: C, 60.83; H, 5.07; N, 19.35. Found: C, 60.59; H, 4.99; N, 19.18.

6-Methoxy-7-aminoquinoxaline (A-26)

A solution of 4.3 g (0.02 mole) of A-25 in 21 ml of 5N HCl was refluxed with stirring for 3 hr. Cooling of the reaction mixture in an ice water bath resulted in the precipitation of a dark brown solid. This was collected by filtration and washed with a small amount of ice water followed by a small amount of 2-propanol to give 4.35 g of solid, m.p. 211-213° dec. This solid was stirred with 30 ml of saturated Na_2CO_3 to yield 4.2 g of crude A-26 as a yellow solid, m.p. 159-161°. One recrystallization from 120 ml of benzene gave 2.2 g (63% yield) of A-26 as yellow crystals, m.p. 162-164°. Two more recrystallizations yielded an analytical sample; ir (KBr): 3400 and 3280 cm^{-1} (NH_2).

$\underline{Anal}$. Calcd for $C_9H_9N_3O$: C, 61.71; H, 5.14; N, 24.00. Found: C, 61.49; H, 5.09; N, 24.05.

6-Methoxy-7-[(5-diethylamino-2-pentyl)amino]quinoxaline (A-28)

A stirred mixture of 6.6 g (0.037 mole) of A-26, 9.2 g (0.045 mole) of 5-diethylamino-2,2-dimethoxypentane, and 150 mg of p-toluenesulfonic acid monohydrate was heated at 165-170° for 2 hr. Methanol, which formed in the process, was distilled during the reaction. The resulting mixture was cooled and diluted with 200 ml of Et_2O, washed with 30 ml of 5% Na_2CO_3 and 30 ml of saturated aqueous NaCl. The Et_2O solution was dried (K_2CO_3) and evaporated to give the crude anil A-27 as a light brown liquid; its ir spectrum had a characteristic C=N absorption at 1660 cm^{-1}.

The crude anil A-27 was dissolved in 100 ml of absoluted EtOH. To the solution, at 0°, was added 4.5 g of $NaBH_4$ in several portions and the mixture was stirred overnight at room temperature. It was then poured into 500 ml of H_2O, extracted with Et_2O (5 x 100 ml), dried ($MgSO_4$), and evaporated to give a liquid. This was dissolved in 10 ml of $CHCl_3$ and column chromatographed over 150 g of silica gel (Woelm, Act I). The mixture was initially eluted with $CHCl_3$-MeOH (9:1). The eluent was monitored with tlc (silica gel, $CHCl_3$-MeOH, 9:1). The first 500-ml portion (a yellow solution) contained both the starting compound A-27 and the product A-28, together with a compound which was not identified. The second 2000-ml portion, eluted with $CHCl_3$-MeOH (3:1), contained mainly the desired product A-28 and a lower-boiling component related to the starting ketal. Evaporation of the second fraction and distillation through the Kügelrohr Distilling Apparatus at 80-85°/0.3-0.35 mm, gave the lower-boiling component, (about 0.8 g). After raising the oven temperature to 120-125°/0.3-0.35 mm, 2.6 g of the target compound A-28 was collected.

The first fraction of the column chromatographic eluent was evaporated, the residue (4.0 g) again column chromatographed, and its second fraction redistilled as described above, giving an additional 2.0 g of A-28. The total yield was therefore 4.6 g (39%); ir (neat): 3420 (NH) and 1620 cm^{-1} (aromatic H); uv: λ $\frac{EtOH}{Max}$ 267 (ϵ 24,000) and 388 nm (ϵ 11,800); nmr (CDCl$_3$): δ 0.98 (6H, $\underline{t}$, J = 7 cps, two CH$_3$ at the ethyl terminal), 1.29 (3H, $\underline{d}$, J = 6 cps, CH$_3$ at the 1-methylbutyl group), 1.46-1.76 (4H, $\underline{m}$, protons at C-2 and C-3 of the butyl group), 2.28-2.64 (6H, $\underline{m}$, three CH$_2$ attached to the tertiary N), 3.40-3.80 (1H, $\underline{m}$, methine proton at C-1 of the butyl group), 3.92 (3H, $\underline{s}$, OCH$_3$), 4.70-4.90 (1H, $\underline{m}$, NH), 6.85 and 7.13 (2H, $\underline{s}$, aromatic protons), 8.35 and 8.45 (2H, $\underline{d}$, J = 2 cps, heteroaromatic protons).

$\underline{Anal}$. Calcd for C$_{18}$H$_{28}$N$_4$O: C, 68.35; H, 8.86; N, 17.72. Found: C, 68.27; H, 8.67; N, 17.56.

4-Methoxy-2-nitroacetanilide (A-30)

A mixture of 252 g (1.5 mole) of 4-methoxy-2-nitroaniline (A-29) (Aldrich), 168 g (1.65 mole) of Ac$_2$O and 400 ml of AcOH was heated at 100° on an oil bath until all solids were dissolved. After cooling to room temperature, the solution was poured into 1,500 ml of ice water. The orange solid was collected and washed with H$_2$O and dried in air to give 300 g (95% yield) of crude A-30. Two recrystallizations from EtOH and H$_2$O gave an analytical sample, m.p. 116° (lit,[12] m.p. 116.5-117°).

$\underline{Anal}$. Calcd for C$_9$H$_{10}$N$_2$O$_4$: C, 51.43; H, 4.76; N, 13.33. Found: C, 51.33; H, 4.68; N, 13.59.

2-Amino-4-methoxyacetanilide (A-31)

To a mechanically stirred suspension of 100 g of iron dust (Fisher, electrolytic), 15 ml of AcOH, and 600 ml of H$_2$O at 65-75° was added portionwise 100 g of A-30 in 1 hr. The reaction mixture was stirred at 65-75° for another hour and filtered while hot through Celite. The filtrate, after standing overnight, deposited 18 g of A-31 as light brown solids. The black solid, which was collected on the funnel from the aforementioned hot filtration, was mixed with 1,000 ml of H$_2$O and heated at 70-80° with stirring for 30 min. The mixture was again filtered hot and from the cooled filtrate another 27 g of A-31 was collected. The combined yield was 45 g (53%). Three recrystallizations from H$_2$O gave an analytical sample, m.p. 147° (lit,[13] m.p. 145°).

$\underline{Anal}$. Calcd for C$_9$H$_{12}$N$_2$O: C, 60.00; H, 6.67; N, 15.55. Found: C, 60.29; H, 6.97; N, 15.61.

4-Methoxy-2-(5-diethylamino-2-pentylamino)acetanilide   (A-33)

A mixture of 1.8 g (0.01 mole) of A-31, 2.2 g (0.011 mole) of 4-diethylamino-2,2-dimethoxypentane (A-19) and a few crystals of p-toluenesulfonic acid was heated with stirring at 160-165° for 3 hr. Methanol, which formed in the process of the reaction, was distilled during the heating. The reaction mixture was then diluted with 100 ml of Et_2O, washed with 20 ml of 5% Na_2CO_3, 20 ml of saturated aqueous NaCl, and dried (K_2CO_3). Evaporation of the Et_2O solution yielded crude 2-acetamido-5-methoxy-N-(5-diethylamino-2-pentylidene)aniline (A-32) as a light brown liquid. A double absorption band around 1660 cm^{-1} (C=O and C=N-) was observed in the ir spectrum. This liquid was stirred with 1.5 g of $NaBH_4$ in 50 ml of absolute EtOH overnight at room temperature. It was then diluted with 250 ml of H_2O, extracted with Et_2O (4 x 100 ml) and dried (K_2CO_3). Evaporation of Et_2O gave a light brown liquid, which was dissolved in 3 ml of $CHCl_3$ and column chromatographed on 100 g of silica gel (Woelm, Act I) eluting with MeOH-$CHCl_3$ (1:3). The first 80-ml portion contained ca. 50 mg of starting compound A-31;the second 225-ml fraction contained no isolable products and was discarded; the third 1000-ml fraction contained 1.6 g of liquid, which was believed to be the crude product A-33 contaminated with a small amount of compound related to the starting ketal; ir: 3370 and 3250 cm^{-1} (NH) and 1650 cm^{-1} (C=O); its nmr ($CDCl_3$) spectrum had, among other peaks, a doublet (J = 6 cps) at δ 1.13 for CH_3 at C-1 of pentyl side chain and a singlet at δ 2.04 for N-acetyl.

1-(p-chlorophenyl)-1,1-dimethoxyethane   (A-38)

A solution of 38.5 g (0.25 mole) of p-chloroacetophenone (Aldrich), 30 g of trimethyl orthoformate, 0.3 g of p-toluenesulfonic acid monohydrate and 100 ml of MeOH was refluxed for 7 hr. The reaction mixture was diluted with 250 ml of 5% Na_2CO_3 extracted with Et_2O (3 x 100 ml) and dried (K_2CO_3). Removal of solvent gave a liquid which, after distillation, gave 26.4 g (53% yield) of the title compound as a colorless liquid, b.p. 53-54°/0.25 mm; ir (neat): 2830 cm^{-1} (OH), no carbonyl absorption around 1700 cm^{-1} was observed; nmr ($CDCl_3$): δ 1.53 (3H, s, CH_3), 3.23 (6H, s, two OCH_3), 7.57 (4H, d, J = 3 cps, aromatic protons).

2-Methoxy-5-nitro-N-(5-phthalimido-4-pentyl)aniline (A-45)

A mixture of 18.5 g (0.11 mole) of 2-methoxy-5-nitroaniline (A-40) and 34 g (0.11 mole) of 1-phthalimido-4-bromopentane (A-44) in 80 ml of EtOH and 18 ml of diisopropylamine was heated in an autoclave at 130° for 15 hr. After cooling, the mixture was poured into H_2O and made basic with NaOH solution. The precipitated solid was filtered, washed with a little MeOH and recrystallized three times from the same solvent. There was obtained 4.2 g (10% yield) of A-45 as yellow crystals, m.p. 115-117°.

Anal. Calcd for $C_{20}H_{21}N_3O_5$: C, 62.65; H, 5.52; N, 10.96. Found: C, 62.55; H, 5.49; N, 10.95.

3-Acetamido-N-[(p-chloro-1-methyl)benzylidene]-4-methoxyaniline (A-50a)

2-Methoxy-5-nitroaniline (A-40), 7.6 g (0.045 mole), was added to 50 ml of Ac_2O with stirring. Yellow crystals of the acetamido compound A-48a rapidly precipitated. The mixture was diluted with H_2O and the solid product filtered after hydrolysis of excess Ac_2O had been completed. The crude product was then dissolved in 200 ml of EtOH and hydrogenated at 50 psig in the presence of Pd/C. The reduction was completed in 15 min. After removal of the catalyst, the solution was evaporated to a sirupy residue A-49a under reduced pressure. It was treated with 12 g (0.06 mole) of p-chloroacteophenone dimethyl ketal and the mixture was heated at 155-165° for 20 min. in the presence of 0.1 g of p-toluenesulfonic acid. The solidified product A-50a was triturated with dilute NaOH solution and filtered. It was recrystallized from MeOH and the analytically pure sample was isolated as yellow crystals, m.p. 188-189°, (5.6 g, 44% overall yield); ir: 6.0, 6.1 μ.

Anal. Calcd for $C_{17}H_{17}ClN_2O_2$: C, 64.45; H, 5.41; N, 8.85. Found: C, 64.59; H, 5.28; N, 9.00.

<u>N-[(p-chloro-1-methyl)benzylidene]-4-methoxy-3-(trifluoroacetamido)aniline</u> (A-50b)

To a solution of 3.4 g (0.02 mole) of 2-methoxy-5-nitroaniline
(A-40) in 30 ml of pyridine was added portionwise, with cooling, 3 ml of
$(CF_3CO)_2O$. After being allowed to stand at room temperature for 15 min,
the mixture was diluted with 100 ml of H_2O and the yellow solid product
A-48b collected by filtration. It was hydrogenated over Pd/C in 100 ml of
EtOH to 50 psig for 15 min. The catalyst was removed and the solution
evaporated to dryness under reduced pressure. The residue A-49b was heated
with 4 g (0.02 mole) of p-toluenesulfonic acid at 155° for 10 min. The
solidified product was triturated with dilute NaOH and filtered. It was
recrystallized from MeOH as pale yellow needles, m.p. 150-152° (3.7 g,
50% yield); ir: 5.8, 6.1 μ.

<u>Anal</u>. Calcd for $C_{17}H_{14}ClF_3N_2O_2$: C, 55.07; H, 3.81; N, 7.56.
Found: C, 54.78; H, 3.75; N, 7.37.

4-Methoxy-2-nitro-1-trifluoroacetanilide (A-52)

To a stirred suspension of 33.6 g (0.2 mole) of 4-methoxy-2-
nitroaniline A-51,(Aldrich), 56 g of anhydrous, Na_2CO_3, and 1,000 ml of
anhydrous Et_2O at 10° was added dropwise 56 ml of $(CF_3CO)_2O$ in 150 ml of
Et_2O in 1 hr. The mixture was stirred at room temperature for another
2 hr. The solid was removed by filtration and the filtrate was washed
with H_2O (5 × 200 ml). After drying ($MgSO_4$) and evaporation of Et_2O,
compound A-52, (44 g, 85% yield) was obtained as yellow needles. Three
recrystallizations from EtOH gave an analytical sample, m.p. 89-95°;
ir (KBr): 3320 cm^{-1} (NH), 1720 cm^{-1} (CO); uv: λ_{max}^{EtOH} 236 (ε 21,400)
and 340 nm (ε 3,400).

<u>Anal</u>. Calcd for $C_9H_7F_3N_2O_4$: C, 40.91; H, 2.65; N, 10.61;
Found: C, 40.80; H, 2.58; N, 10.33.

2-Amino-4-methoxy-1-trifluoroacetanilide (A-53)

A solution of 14.2 g (0.054 mole) of A-52 in 200 ml of benzene
was hydrogenated in the presence of 0.6 g of 5% Pd/C under 40 psig of
H_2 for 2 hr. Catalyst was removed by filtration through Celite and the
filtrate was evaporated to give A-53 as a pale yellow solid (12.2 g, 94%
yield), m.p. 90-95°. Three recrystallizations from benzene gave an
analytical sample, m.p. 109-112°, ir (KBr): 3980, 3390, 3240 cm^{-1} (NH),
1710 cm^{-1} (C=O).

<u>Anal</u>. Calcd for $C_9H_9F_3N_2O_2$: C, 46.15; H, 3.85; N, 11.96.
Found: C, 46.30; H, 3.81; N, 11.88.

N-(4-Anisyl)-p-toluenesulfonamide

To a stirred solution of 12.3 g (0.1 mole) of p-anisidine in 25 ml of dry pyridine was added portionwise during a 10-min interval 19.0 g (0.1 mole) of recrystallized tosyl chloride. The resulting mixture was heated at 100° for 3 hr. It was cooled and poured into 400 ml of cold water. After standing 1 hr, the precipitated solid was collected by filtration and dried to give 22 g (80% yield) of crude product, m.p. 109-110° (lit.,[17] m.p. 114°). The product was used for the preparation of the nitro compound A-69 (see Method B under A-69) without further purification.

N-(4-methoxy-2-nitrophenyl)-p-toluenesulfonamide (A-69)

Method A. To a stirred solution of 16.8 g (0.1 mole) of 2-nitro-p-anisidine (A-51) in 50 ml of dry pyridine was added portionwise 19.0 g (0.1 mole) to tosyl chloride (recrystallized from $CHCl_3$-petroleum ether) during 10 min. The mixture was heated at 110° for 3 hr, cooled, and poured, with stirring, into 400 ml of cold water. After 1 hr of stirring, the resulting solid was collected by filtration and recrystallized from 200 ml of methanol to give 25 g (78% yield) of A-69 as an orange solid, m.p. 98-99° (lit.,[15] m.p. 102-103°, lit.,[17] m.p. 104°).

Anal. Calcd. for $C_{14}H_{14}N_2O_5S$: C, 52.16; H, 4.38; N, 8.69. Found: C, 51.90; H, 4.43; N, 8.48.

Method B. To a stirred mixture of concentrated nitric acid and 14 ml of acetic acid at 5° was added a solution of 27.7 g (0.1 mole) of N-(4-anisyl)-p-toluenesulfonamide in 60 ml of acetic acid. The mixture was stirred at 5° for 2 hr, after which the solid was collected by filtration, washed with water, and dried to give 21 g (65% yield) of A-69, m.p. 99-100°. Its ir was identical with that of the product obtained by Method A.

4-Bromo-3-nitroanisole (A-73)

A mixture of 33.6 g (0.2 mole) of 2-nitro-p-anisidine (A-51) in a solution of 60 ml of concentrated H_2SO_4 and 200 ml of water was stirred at 5°. To this was added a solution of 14 g (0.2 mole) of $NaNO_2$ in 40 ml of water. After 2 hr the mixture was clarified by filtration and the filtrate added to a boiling mixture of 200 ml of water, 13 g of $CuSO_4$, 31 g of NaBr, and 4 g of electrolytic copper powder. The resulting mixture was boiled with stirring for 30 min, cooled, and extracted with ether (3 x 100 ml). The ether extract was washed with water, dried, and evaporated. The remaining dark residue was distilled at 120-123°/1.5 mm to give 23 g (50% yield) of an orange liquid, which solidified on standing, m.p. 32° (lit.,[19] m.p. 32°).

N-(3,4-Dimethoxyphenyl-p-toluenesulfonamide (A-74)

The product was prepared from 0.1 mole of 4-aminoveratrole by essentially the same procedure as that used for the preparation of N-(4-anisyl)p-toluenesulfonamide; the yield of A-74 was 84%, m.p. 135-136° (recrystallized from MeOH) (lit.,[44/] m.p. 139°).

Anal. Calcd for $C_{15}H_{17}NO_4S$: C, 58.61; H, 5.68; N, 4.56. Found: C, 58.85, H, 5.60; N, 4.68.

N-[4,5-Dimethoxy-2-nitro)phenyl]-p-toluenesulfonamide (A-75)

To a stirred mixture of 23 g (0.075 mole) of A-74 in 50 ml of AcOH at 15° was added a solution of 8.6 g of concentrated HNO_3 and 11 ml of AcOH. After stirring overnight at room temperature, the solid product, which separated during the reaction, was collected by filtration. It was washed with water, dried, and recrystallized from toluene to give 12 g (46% yield) of analytically pure A-75, m.p. 197-199° (lit.,[45/] m.p. 203-204°).

Anal. Calcd for $C_{15}H_{16}N_2O_6S$: C, 51.13; H, 4.58; N, 7.95. Found: C, 51.29; H, 4.76; N, 8.00.

4-Bromoveratrole (A-80)

A mixture of 69 g (0.5 mole) of veratrole, 80 ml of CCl_4, and 8⁰ g (0.5 mole) of N-bromosuccinimide was refluxed for 6 hr. It was cooled and filtered through a sintered glass funnel. The filtrate was evaporated under reduced pressure and the residue distilled at 102-109°/2 mm to give 93 g (86% yield) of A-80 (lit.,[46/] b.p. 117-120°/5 mm).

4-Bromo-5-nitroveratrole (A-81)

To 70 ml of concentrated HNO_3 at 10° was added, with stirring, 21.7 g (0.1 mole) of A-80 in 30 ml of AcOH during 20 min. The temperature of the reaction mixture rose to 40°. It was stirred for an additional 30 min and poured into 100 ml of ice water. The resulting mixture was stirred for 40 min and the separated solid product was collected by filtration. This was washed well with water and dried to give 20 g of A-81, m.p. 119-121°. Recrystallization from ethanol gave 17 g (65% yield) of pure A-81, m.p. 120-121° (lit.,[47/] m.p. 123°).

4,5-Dinitroveratrole (A-82)

To a stirred mixture of 138 g (1.0 mole) of veratrole in 200 ml
of AcOH at 15° was added 68 ml (96 g) of concentrated HNO_3 during 30 min.
The temperature during addition was kept below 40°. After stirring for
15 min, 300 ml of fuming HNO_3 was added during 30 min and the temperature
was kept below 30°. The resulting mixture was stirred for 2 hr and poured
into 2,000 ml of ice water. The separated solid was collected by filtration,
washed well with water, and dried to give 210 g of A-82, m.p. 120-122°.
Recrystallization from a 3:2 mixture of ethanol and 2-butanone gave 180 g
(80% yield) of pure A-82, m.p. 125-126° (lit.,[48] m.p. 130-132°).

4,5-Diaminoveratrole Dihydrochloride (A-83)

A mixture of 18 g (0.08 mole) of A-82, 200 ml of absolute ethanol,
and 0.5 g of 5% Pd/C was hydrogenated on a Parr Hydrogenator at 65 psig.
After 5 hr the required amount of H_2 was absorbed. The reaction mixture
was heated to almost boiling and filtered. To the filtrate was added a
calculated amount of ethanolic HCl followed by addition of 100 ml of ether.
The hydrochloride salt was collected by filtration and washed with ether
to give 14 g (74% yield) of A-83, m.p. 264-265° dec.

5,6-Dimethoxybenzimidazole (A-84)

A stirred mixture of 12 g (0.05 mole) of A-83 and 70 ml of 98%
HCO_2H was refluxed for 2 hr. It was cooled at 0" and neutralized with
concentrated NH_4OH. The resulting solid was collected by filtration, washed
with ethanol, and dried to give 5 g of an orange solid, m.p. 180-182°.
Recrystallization once from 2-propanol and twice from acetone gave 2.6 g
(29% yield) of pure A-84 as a white solid, m.p. 184-185° (lit.,[49] m.p. 179-
183°).

Anal. Calcd for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66; N, 15.72. Found:
C, 60.22; H, 5.52; N, 15.29.

Attempted preparation of A-84 by refluxing 9.6 g of A-83, 50 ml
of triethyl orthoformate, and 50 ml of Ac_2O gave 6 g of a tan solid,
m.p. 178-180°. Its ir showed strong carbonyl absorption at 5.8 μ but no
NH absoprtion.

4-[(5-diethylamino-2-pentyl)amino]-5-nitroveratrole (A-77)

A mixture of 11.4 g (0.05 mole) of 4,5-dinitroveratrole (A-82)
and 8.7 g (0.055 mole) of novoaldiamine(A-19) was stirred and heated
slowly to 85° under nitrogen, at which temperature the reactants became
one phase. After the mixture was maintained at 85° for 1 hr, it
was heated at 110-115° for 6 hr and cooled. The thick, black syrup was
diluted with 75 ml of EtOAc, charcoaled, and filtered. The filtrate was
evaporated to a syrup and diluted with 15 ml of benzene. This was chromato-
graphed through a silica gel (MCB) column. Elution with petroleum ether
recovered 2 g of starting material A-82. Continued elution with benzene
and benzene-EtOAc mixture gave 10 g (62% yield) of A-77 as a dark orange oil.
IR: 3.0 μ (NH), 6.1 μ, 6.3 μ, and 6.6 μ. UV: $\lambda_{Max}^{pH\ 1,11}$ 240 nm (ϵ 18,400)
and 324 nm (ϵ 8,100). NMR (CDCl$_3$): δ 1.0 (t, J = 7Hz, CH$_2$CH$_3$), 1.32
(d, J = 7Hz, CH-CH$_3$), 1.48-1.87 (m, CH$_2$), 2.52 (q, J = 6 Hz, CH$_2$-CH$_3$),
3.85 (s, OCH$_3$), 3.95 (s, OCH$_3$), 6.23 (s, aromatic H), 7.62 (s, aromatic H),
8.46 (broad, NH).

N-(4-Bromopentyl)phthalimide (A-87)

A mixture of 25.3 g (0.11 mole) of 1,4-dibromopentane, 18.5 g
(0.1 mole) of potassium phthalimide, and 75 ml of acetone was stirred and
refluxed for 20 hr. It was filtered and the filtrate evaporated and
distilled. There was obtained 18 g (60% yield) of A-87, b.p. 154-156°/0.05 mm
(lit.,[50] b.p. 165-167°/0.25 mm).

N-Chloroacetyl-D,L-leucine (B-2)

A suspension of 50 g (0.38 mole) of D,L-leucine (B-1, Aldrich),
85 g (0.76 mole) of chloroacetyl chloride and 500 ml of EtOAc was refluxed
with stirring for 40 min until all solids dissolved. The reaction mixture
was poured into an evaporating dish and evaporated under a stream of air to
yield 79 g of a light yellow solid, m.p. 90-115°. Two recrystallizations
from EtOAc gave 52.5 g (67% yield) of analytically pure B-2, m.p. 134-136°
(lit.,[22] m.p. 142°); ir (KBr): 3350 cm^{-1} (NH), 3600-2300 cm^{-1} (carboxylic
OH), and 1710 and 1620 cm^{-1} (two C=O).

Anal. Calcd. for C$_8$H$_{14}$ClNO$_3$: C, 46.27; H, 6.80; N, 6.75. Found:
C, 46.47; H, 6.99; N, 6.79.

4-Isobutylidene-2-methyloxazol-5-one (B-3)

A stirred mixture of 40 g (0.19 mole) of B-2 and 60 ml of Ac_2O was heated at 60° for 90 min. Excess Ac_2O was removed under reduced pressure and the residual liquid was distilled in vacuo. The fraction collected at 55-56°/0.45 mm (lit.,[21] b.p. 68-69°/0.15 mm), 15 g (52% yield), was the expected product; ir (neat): 1800, 1690, and 1640 cm^{-1}; nmr (CDCl$_3$): δ 1.11 (d, J = 6 cps, 6H, gem-dimethyl), 2.06 (s, 3H, methyl gp on C-2), 2.92-3.34 (m, 1H, methine proton), 6.31 (d, J = 10 cps, 1H, vinyl proton. The product was unstable on standing.

N-Acetyldehydroleucine (B-4)

A mixture of 10 g (0.065 mole) of the oxazolone B-3 and 24 ml of H_2O was kept at 0° overnight. The precipitated solid was collected by filtration and dried in air to give 8.0 g (72% yield) of crude B-4, m.p. 145-152°. Recrystallization from EtOAc gave 6.4 g (58% yield) of analytically pure B-4 as white crystals, m.p. 152-153° (lit.,[5] m.p. 155-157°); ir (KBr): 3280 cm^{-1} (NH), 3500-2300 cm^{-1} (carboxylic OH), 1700 cm^{-1} (CO), and 1660 cm^{-1} (CO); nmr (DMSO-d$_6$): δ 0.97 (d, J = 6 cps, 6H, gem-dimethyl), 1.94 (s, 3H, methyl group of CH$_3$CONH), 2.28-2.80 (m, methine proton), 4.88 (s, water peak), 6.28 (d, J = 10 cps, 1H, vinyl proton), 8.86 (s, 1H, NH).

Anal. Calcd. for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 55.81; H, 7.79; N, 8.21.

N-(p-Chlorobenzoyl)-D,L-threonine (B-6)

The method of preparation of hippuric acid[23] was followed for the present preparation. To a stirred solution of 25 g (0.195 mole) of D,L-threonine (B-5) hemihydrate in 125 ml of H_2O was added simultaneously, through two dropping funnels, 27.4 ml of p-chlorobenzoyl chloride and 16.5 g (0.4 mole) of NaOH in 80 ml of H_2O in a period of 1 hr. The addition was kept at such a rate that the reaction mixture remained slightly basic and the temperature was below 27° throughout the reaction. The resulting mixture was stirred at room temperature for another hour, then acidified with 25 ml of concentrated HCl. The precipitated solid was collected by filtration, washed with H_2O and dried in air to give 48 g of crude B-6, m.p. 170-180° dec. Recrystallization from 120 ml of 40% EtOH gave 43 g (86% yield) of pure B-6 as white crystals, m.p. 170-171° dec. The structural assignment was based on its ir spectrum, which had a characteristic carbonyl absorption for carboxylic acid at 1710 cm^{-1} and carbonyl absorption for amide at 1640 cm^{-1} and 1530 cm^{-1}.

Anal. Calcd. for $C_{11}H_{12}ClNO_4$: C, 51.27; H, 4.69; N, 5.44. Found: C, 51.03; H, 4.63; N, 5.24.

2-(p-Chlorophenyl)-4-ethylideneoxazol-5-one (B-7)

The method of Carter et al.[24] for the preparation of unsaturated
azlactone was followed. To a solution of 25.7 g (0.1 mole) of B-16 in 200 ml
of anhydrous pyridine at 0° was added dropwise 26 g (0.2 mole) of benzoyl
chloride in 30 min. The reaction mixture was stirred at 0° for an additional
40 min, then poured into a mixture of 200 ml of concentrated HCl and 800 g
of ice water. The resulting precipitate was collected by filtration, washed
with ice water, and dried in air to give 33.5 g of crude B-7 as a white solid,
m.p. 110-137°. Recrystallization from 110 ml of MeOH gave 18.5 g (84% yield)
of pure B-7 as white needles, m.p. 154-156°, ir (KBr): 1790, 1670, and 1590 cm^{-1};
nmr ($CDCl_3$): δ 1.20 and 1.30 (two doublets with a ratio of 4.5:1, J = 8 cps,
3H, methyl group), 6.68 (q, J = 8 cps, 1H vinyl proton, a small peak was also
noticed at 6.88), 7.40 and 7.96 (an AB pattern of two distorted doublets,
J = 10 cps, 4H, aromatic protons).

Anal. Calcd. for $C_{11}H_8ClNO_2$: C, 59.60, H, 3.64, N. 6.32. Found:
C, 59.40, H, 3.81; N, 6.12.

2-(p-Chlorobenzamido)crotonic Acid (B-8)

A stirred mixture of 12.4 g (0.05 mole) of B-7 and 100 ml of
1N NaOH was heated at 60-70° until all solid dissolved (ca. 40 min). The
resulting solution was cooled in an ice-water bath and acidified in 5N HCl.
The precipitate was collected by filtration, washed with cold water and dried
in air to give 12.5 g of crude B-8, m.p. 200-205° dec. Recrystallization from
400 ml of EtOAc gave 5.5 g (46% yield) of B-8 as white crystals, m.p. 213-
215° dec.; ir (KBr): 3250 cm^{-1} (NH), 3600-2400 cm^{-1} (carboxylic OH), 1690 cm^{-1}
(CO), and 1650 cm^{-1} (CO).

Anal. Calcd. for $C_{11}H_{10}ClNO_3$: C, 55.13; H, 4.21; N, 5.85. Found:
C, 55.09; H, 4.17; N, 5.87.

2-Tetrahydrothiophenemethanol (C-2)

To a stirred, refluxing solution of 77 ml (0.26 mole) of 70%
RED-AL in benzene and 75 ml of ether was added a solution of 27 g (0.17
mole) of ethyl tetrahydrothiophenecarboxylate (C-1a) in 175 ml of ether
during 30 min. The mixture was stirred for 2 hr and excess reducing agent
carefully decomposed with a solution of 13 ml of concentrated sulfuric
acid in 50 ml of water. The resulting reaction mixture was diluted with
250 ml of methanol and refluxed for 10 min. The insoluble salts were

removed by filtration and the filtrate was concentrated to a small volume.
To this was added 100 ml of ether. The mixture was again filtered and the
filtrate dried and evaporated to an oil. This was subjected to fractional
distillation and the initial fraction (8 g) was collected at 71-85°/155 mm.
A glc-mass spec determination revealed that the liquid was a mixture of
three components, none having a molecular ion higher than 102 (the mole-
cular weight of C-2 is 118). The next fraction, collected at 120-122°/
30 mm was found to be the desired methanol C-2. This preparation will
be repeated for the synthesis of compound C-5.

Methyl 3-methyl-2-furoate[5/] (C-9)

This compound was prepared according to the literature method[25/]
with the following modification: Sodium hydride and a catalytic amount of
ethanol was used as a base instead of sodium methoxide for the Darzen's
glycidic ester condensation. Thus, one-third of a solution of 4,4-dimethoxy-
2-butanone (132 g, 1 mole) and methyl chloroacetate (174 g, 1.6 mole) was
added to a stirred mixture of 77 g of sodium hydride (50% in mineral oil)
in 800 ml of anhydrous ether at -5°. To this stirred mixture was then added
1.5 ml of absolute ethanol and the temperature of the reaction mixture was
allowed to rise to 10° to effect the reaction. The course of the reaction
was followed by measurement of hydrogen evolved. The reaction temperature
was maintained below 10° so that the reaction could be kept under control.
When the evolution of hydrogen slowed, the remaining two-thirds of the
solution of 4,4-dimethoxy-2-butanone and methyl chloroacetate was added
dropwise into the mixture during 2 hr. The resulting mixture was stirred
at room temperature for 6 hr and allowed to stand overnight. It was acidi-
fied with 20% acetic acid and the organic layer was separated. The aque-
ous layer was extracted with ether (3 x 200 ml). The combined ether ex-
tracts and the organic layer were dried over magnesium sulfate; evaporation
of ether gave a dark brown liquid. This was distilled at an oil-bath tem-
perature of 140° and two fractions of colorless liquid were collected.
The first 8-g fraction, collected at 65-95°/3-4.5 mm, consisted of methyl
3-methylfuroate (C-9) and unrearranged glycidic ester C-8 in a 1 1 ratio,
as shown in the nmr spectrum; the second 73-g fraction, collected at 103°/
4.5-8 mm, contained 67% of the desired ester C-9. Redistillation of the
first fraction with 5 drops of acetic acid gave 4.2 g of pure methyl
3-methylfuroate (C-9), b.p. 90°/4.5 mm (Lit.[5/] b.p. 72-78°/8 mm); nmr
(CDCl$_3$): δ 2.35 (s, 3H, CH$_3$), 3.90 (s, 3H, OCH$_3$), 6.42 (d, J=2 cps, 1H,
aromatic proton at C-4), 7.55 (d, J=2 cps, 1H, aromatic proton at C-5); ir
(neat): 1710 cm^{-1} (C=O). Since redistillation of the first fraction did
not increase the yield of pure C-9, the second fraction was not redistilled
and was used directly for the preparation of 3-methyl-2-furoic acid (C-10).
The overall yield of C-9 through the condensation and rearrangement reac-
tion was 53%.

3-Methyl-2-furoic Acid (C-10)

The second fraction of the aforementioned distillate, which was estimated to contain 50 g (0.35 mole) of the ester C-9, was refluxed and stirred with 170 ml of 20% sodium hydroxide for 3 hr. After being cooled to room temperature, the reaction mixture was extracted with ether (2 x 100 ml) and the remaining aqueous solution acidified with concentrated hydrochloric acid to yield a solid. This was collected by filtration, washed with water and dried at 75° in a vacuum oven overnight. There was obtained 40 g (90%) of C-10, m.p. 127-128° (Lit,[26] m.p. 134-135°). An analytically pure sample was prepared by sublimation at 60°/0.1 mm, m.p. 127-128°.

Anal. Calcd. for $C_6H_6O_3$: C, 57.14; H, 4.76. Found: C, 56.85; H, 4.84.

3-Methylfuran (C-11)

A mixture of 76 g (0.6 mole) of C-10, 13.5 g of copper dust (electrolytic), and 150 ml of quinoline (distilled over BaO) was stirred and heated to 240°. The product, 3-methylfuran (C-11), was allowed to distill through a 30-cm Vigreux column. After 3 hr of heating, 43 g of C-11 was collected. Redistillation of the product afforded 42.5 g (87% yield) of pure C-11, b.p. 66.5-68.5° (Lit,[26] b.p. 65.5-66°), nmr (neat) δ 1.9 (s, 3H, CH_3), 6.2 (s, 1H, aromatic proton at C-6), 7.2 and 7.3 (two s, 2H, aromatic protons at C-2 and C-5).

3-Methylfuran-2-carboxaldehyde (C-12)

A literature method[27] was followed for the preparation of this compound. Thus, 42 g (0.51 mole) of C-11 was added dropwise to a stirred solution of 107 g of phosphorus oxychloride and 51 ml of dry dimethylformamide at 0° during 70 min. The resulting mixture was stirred between 2-10° for an additional 50 min and allowed to rise to room temperature. It was then stirred at room temperature for another 40 min followed by heating on a water bath (38-40°) for 20 min. The reaction mixture was poured, with stirring, onto 600 g of crushed ice and the resulting mixture neutralized with 185 g of sodium carbonate. The mixture was extracted with ether (1 x 400 ml + 3 x 200 ml) and the ether extracts were combined and dried (MgSO4). Evaporation of ether and distillation of the residue gave 44.7 g (80% yield of a colorless liquid, b.p. 77.5-80.5°/7 mm (lit,[27] b.p. 58-60°/11 mm), which contained the desired 3-methylfuran-2-carboxaldehyde (C-12) the isomeric 4-methylfuran-2-carboxaldehyde, and an impurity in a ratio of 30:4:1, as described in the literature.[27] Its ir spectrum showed an aldehydic C=H stretching band at 2780 cm^{-1} and a carbonyl band at 1680 cm^{-1}. No further work was done to determine its composition or to isolate the desired aldehyde C-12. The liquid was used directly for the next reaction.

5-(3-Methyl-2-furyl)hydantoin (C-13)

A solution of 26 g (0.24 mole) of the aforementioned distillate, 76 g (0.95 mole) of ammonium carbonate and 400 ml of 60% aqueous ethanol was heated, with stirring, on a water bath at 50° for 10 min. To the solution was added a solution of 16.2 g (0.25 mole) of potassium cyanide in 35 ml of water and the resulting mixture stirred at 50-55° for 12 hr. Most of the ethanol was then evaporated and the remaining aqueous solution was cooled to room temperature. This was extracted with ether (3 x 100 ml). The aqueous layer was cooled in an ice-water bath and acidified with 5N hydrochloric acid to yield 25.5 g of a brown solid, m.p. 118-123°. The latter was dissolved in 40 ml of boiling 40% aqueous ethanol, decolorized with 0.5 g of activated charcoal, filtered and cooled at 0° for 2 hr. There was obtained 20 g of yellow-brown crystals, m.p. 130-134°. The solid was dissolved in 60 ml of acetone and column chromatographed over 100 g of silica gel, eluting with chloroform-acetone (3:1). The first 900-ml fraction was found to contain 19.5 g (46% yield) of the hydantoin C-13, m.p. 140-142°. Two recrystallizations from 50% aqueous ethanol yielded an analytical sample, m.p. 143-144°; ir (KBr): 3400, 3300-2900 cm^{-1} (broad), 1770-1670 cm^{-1}.

<u>Anal</u>. Calcd. for $C_8H_8N_2O_3$: C, 53.33; N, 4.44; N, 15.55. Found: C, 53.62; H, 4.36; N, 15.53.

2-Amino-2-(3-methyl-2-furyl)acetic Acid (C-14)

In a 300-ml steel vessel was placed 42 g (0.15 mole) of Ba(OH)$_2$·8H$_2$O, 220 ml of water and 17 g (0.095 mole) of C-13. The container was sealed and heated to 150° in 6 hr and maintained at that temperature for 2 hr. After cooling, the reaction mixture was transferred to a beaker by rinsing with 180 ml of water. The resulting mixture was heated at 60° for 90 min to remove excess ammonia. The mixture was filtered, the filtrate acidified with 5M sulfuric acid to pH 6 and the precipitated barium sulfate removed by filtration. The filtrate was then evaporated <u>in vacuo</u> to yield a white solid residue. Recrystallization of the solid from 70% aqueous ethanol gave 7.1 g (48% yield) of the amino acid C-14, m.p. 181-185° dec. An additional recrystallization from the same solvent yielded an analytical sample, m.p. 180° dec; ir (KBr) 3500-2300, 1650 cm^{-1}.

<u>Anal</u>. Calcd. for $C_7H_9NO_3$: C, 54.19; H, 5.81; N, 9.03. Found: C, 54.47; H, 5.67, N, 9.02.

2-Amino-2-(3-methyl-2-tetrahydrofuryl)acetic Acid (C-15)

To a solution of 5 g (0.03 mole) of C-14 in 200 ml of 40% aqueous ethanol was added 1.2 g of 10% Pd/C. The mixture was hydrogenated at 30 psig for 24 hr. The catalyst was removed by repeated filtration through Celite and the clear filtrate evaporated in vacuo to yield a white solid. Recrystallization from 70 ml of 85% aqueous ethanol gave 1.0 g (20% yeild) of the reduced amino acid C-15 as cotton-like crystals, m.p. 205-206° dec. An additional recrystallization afforded an analytical sample, m.p. 207-208° dec; ir (KBr): 3550-3250, 3150, 3050-2300 and 1620 cm^{-1}.

Anal. Calcd. for C$_7$H$_{13}$NO$_3$: C, 52.83; H, 8.18; N, 8.81. Found: C, 53.04; H, 8.33; N, 8.52.

The mother liquor was concentrated in vacuo to 20 ml and chilled at 2" overnight; a different type of crystalline solid was obtained, m.p. 207-208°. Although the melting point of a mixture of two products was not depressed, the ir spectrum of the second product was different from the first one; ir (KBr): 3550-3300, 3300-2300 and three strong absorption bands at 1660, 1580 and 1490 cm^{-1}. Both products gave positive ninhydrin tests. The second product, 0.6 g, has not yet been identified.

Ethyl p-chlorobenzoylacetate (C-20)

A mixture of 92.5 g (0.5 mole) of ethyl p-chlorobenzoate (C-19) and 48 g (1 mole) of sodium hydride-mineral oil dispersion in 500 ml of benzene was heated under reflux for 1 hr. Ethyl acetate (44 g, 0.5 mole) was then added dropwise, with stirring, over a period of 30 min. Heating was continued for 5 hr, as the reaction mixture was gradually getting thick. It was thoroughly cooled and treated with a methanol-ether mixture to decompose excess sodium hydride. The mixture was cautiously poured over crushed ice, with stirring, and acidified with 120 ml of acetic acid. After the precipitated solid (p-chlorobenzoic acid) was filtered, the benzene layer was separated from the aqueous layer and the latter extracted with ether. The combined organic layer was washed with water, cooled and filtered once more to remove residual p-chlorobenzoic acid. Solvent was removed from the filtrate by distillation and the residue was distilled in vacuo to afford 49.5 g (43% yield) of ethyl p-chlorobenzoylacetate (C-20) as a colorless oil, b.p. 110-115°/0.8 mm.

α-(p-Chlorobenzoyl)-γ-butyrolactone (C-21)

Method A

To a cooled (ice bath) sodium ethoxide solution prepared from 14.3 g (0.62 g atom) of sodium and 500 ml of ethanol was added 143 g (0.62 mole) of ethyl p-chlorobenzoylacetate (C-20), with stirring, over a period of 30 min. It was followed by 32 g (0.73 mole) of ethylene oxide. The ice bath was removed and the reaction mixture stirred at room temperature under a Dry Ice condenser for 3 hr. The reaction mixture was poured into water (300 ml) and neutralized with dilute sulfuric acid. After 2 days, long white needles were formed and were collected by filtration (30 g, 21% yield), m.p. 68-70°. It was recrystallized from benzene, m.p. 68-70° (Lit,[31] 70-71°).

Anal. Calcd. for $C_{11}H_9ClO_3$ (224.63): C, 58.81; H, 4.04. Found· C, 59.06; H, 4.11.

Method B

Balani and Kulkarni's method[31] was generally followed in this experiment as well as in the one described under Method C. To a stirred suspension of 23 g (0.5 mole) of sodium hydride-mineral oil dispersion in 400 ml of benzene was added a few milliliters of α-acetyl-γ-butyrolactone (C-24). The mixture was warmed briefly until the reaction was initiated. The remainder of a total of 64 g (0.5 mole) of C-24 was added slowly to maintain refluxing of the solvent. The mixture was heated with stirring for 4 hr. It was then cooled in an ice bath, and 87.5 g (0.5 mole) of p-chlorobenzoyl chloride in 100 ml of benzene was added over a period of 30 min. The reaction mixture was heated at 40° for 1 day. After cooling, the benzene solution was filtered, washed with sodium bicarbonate and water, and concentrated to 100 ml. The precipitated p-chlorobenzoic acid was filtered and the filtrate evaporated to dryness. The solid residue was triturated with Skelly F. On filtration, there was obtained 67 g (50% yield) of α-acetyl-α-(p-chlorobenzoyl)-γ-butyrolactone (C-25) as a white solid, m.p. 95-105°. It was recrystallized from acetone, m.p. 108-109° (Lit,[31] 112°).

Anal. Calcd. For $C_{13}H_{11}ClO_4$ (266.67): C, 58.55; H, 4.16. Found: C, 58.39; H, 3.99.

For deacetylation, 2.67 g (0.01 mole) of C-25 was heated with 1.28 g of ammonium chloride and 5 ml of ammonium hydroxide at 50° for 1 hr. The solid, which separated on cooling, was filtered, m.p. 60-65° (0.9 g, 40% yield). After recrystallization from benzene, it melted at 68-70°, identical with the product obtained by Method A.

Method C

Magnesium turnings, 14.4 g (0.61 g atom), were allowed to react with 15 ml of ethanol and 3 ml of carbon tetrachloride. As the reaction started, 100 ml of benzene was introduced. When the initial reaction subsided, a solution of 115 g (0.9 mole) of α-acetyl-γ-butyrolactone (C-24) in 75 ml of benzene and 60 ml of ethanol was added, with stirring, at such a rate that a gentle reflux of the solvent was maintained (total addition time: 1 hr). The reaction mixture was heated for 3 additional hr. After having been cooled in ice water for 30 min, the mixture was treated with 158 g (0.9 mole) of p-chlorobenzoyl chloride in 100 ml of benzene (30 min). The cooling bath was removed, and the mixture was heated at 50° for 2 hr. It was then allowed to stand at room temperature for 2 days before being neutralized with dilute sulfuric acid. The benzene layer was separated, washed with water and concentrated. There was obtained an initial crop of the product C-21 (82 g). Further evaporation of the mother liquor afforded additional 25 g of the desired product, m.p. 63-68°. The total yield was 107 g (53%). It was shown to be identical with the products obtained by Methods A and B.

4-Bromo-4'-chlorobutyrophenone (C-22)

α-(p-chlorobenzoyl)-γ-butyrolactone, 112.5 g (0.5 mole), was heated on steam bath with 350 ml of 48% hydrobromic acid for 4 hr. After cooling, the oily layer was separated and the aqueous layer extracted with 200 ml of benzene. The combined organic layer was washed with water, filtered and the filtrate evaporated *in vacuo* to leave a residue of 115 g (88% yield). This crude product was distilled under reduced pressure to give a colorless liquid, b.p. 130°/1 mm, which turned yellow on standing.

Anal. Calcd. for $C_{10}H_{10}BrClO$ (261.54): C, 45.92; H, 3.85. Found: C, 46.20; H, 3.84.

2-(p-Chlorophenyl)-2-cyanotetrahydrofuran (C-23)

A mixture of 78.5 g (0.3 mole) of 4-bromo-4'-chlorobutyrophenone (C-22) and 30 g (0.33 mole) of cuprous cyanide in 300 ml of benzene was heated under reflux for one day. Infrared spectrum of the reaction mixture showed that the reaction was not yet complete, thus another 3 g of cuprous cyanide was added, and the reaction mixture was heated for additional 7 hr. The solid was filtered and the benzene solution evaporated. The residue was distilled *in vacuo* to give a main fraction boiling at 120-130°/1.5 mm which corresponded to the desired product (27 g, 43% yield).

53

This fraction was redistilled to yield a colorless oil, b.p. 123°/1.5 mm, which gradually turned to yellowish green on standing.

Anal. Calcd. for $C_{11}H_{10}ClNO$ (207.65): C, 63.62; H, 4.85; N, 6.75. Found: C, 63.58, 63.35; H, 4.50, 5.07; N, 5.37, 5.52.

2-(p-Chlorophenyl)tetrahydrofuran-2-carboxaldehyde Semicarbazone (C-26)

A mixture of 10.4 g (0.05 mole) of 2-(p-chlorophenyl)-2-cyano-tetrahydrofuran (C-21), 5.57 g (0.05 mole) of semicarbazide hydrochloride, and 5.5 g (0.04 mole) of sodium acetate trihydrate in 100 ml of ethanol and 50 ml of water was hydrogenated at 50 psig in the presence of Raney nickel catalyst. The hydrogenation was completed in 4 hr with absorption of one equivalent of hydrogen. The supernatant solution was decanted and the residual solid was boiled with 200 ml of ethanol. After all product dissolved, the catalyst was removed by filtration. The filtrate was combined with the decanted solution and concentrated. The precipitated solid product was collected by filtration (12 g, 45% yield), m.p. 175-180°. It was recrystallized from methanol as white crystals, m.p. 186-188°.

Anal. Calcd. for $C_{12}H_{14}ClN_3O_2$ (267.68): C, 53.84; H, 5.27; N, 15.69. Found: C, 53.63; H, 5.36; N, 15.39.

Diethyl Anilinomethylenemalonate (D-7)

Diethyl ethoxymethylenemalonate, 238 g (1.1 moles), was added in several portions to 93 g (1 mole) of aniline in an evaporating dish. After the initial exothermic reaction subsided, the mixture was allowed to stand at room temperature for 30 min then evaporated under a stream of air. The solid product was collected by filtration and washed with Skelly F. There was obtained 205 g (78% yield) of C-6 as beige crystals, m.p. 41-45°. Recrystallization from acetone-cyclohexane yielded pure C-6 as white crystals, m.p. 46-48° (lit.,[51] m.p. 48°).

Anal. Calcd. for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.67; H, 6.47; N, 5.45.

Ethyl 4-Hydroxy-3-quinolinecarboxylate (D-8)

Into 800 ml of Dowtherm preheated at 240° was added portionwise 315 g (1.2 moles) of D-7. Heating was continued for 30 min after the addition.

On cooling, the product D-8 crystallized. It was collected by filtration and washed with Skelly F to give 125 g (45% yield) of crude D-8, m.p. 268-272°. A small sample was recrystallized from MeOH as off-white crystals, m.p. 267-270° (lit.,[52] m.p. 266-267°).

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.31; H, 5.19; N, 6.54.

Ethyl 4-Chloro-3-quinolinecarboxylate (D-9)

A mixture of 30 g of D-8 and 35 ml of $POCl_3$ was refluxed for 3 hr. After standing overnight at room temperature the mixture was poured, with stirring, onto crushed ice and made basic with NH_4OH. The crude product readily solidified and was collected by filtration to give 22.5 g (70% yield) of D-9, m.p. 43-45°. Recrystallization from Skelly F gave pure D-9 as white plates, m.p. 45-46° (lit.,[53] m.p. 46-47°).

Anal. Calcd. for $C_{12}H_{10}ClNO_2$: C, 61.16; H, 4.28; N, 5.94. Found: C, 60.88; H, 4.43; N, 6.08.

Methyl 4-Methoxy-3-quinolinecarboxylate (D-10)

To a methanolic sodium methoxide solution prepared from 6 g of Na and 350 ml of MeOH was added 42 g (0.178 mole) of D-9 in small portions. After the addition was complete, the mixture was refluxed for 1 hr with stirring. It was then diluted with 1 liter of cold water and the solvent evaporated under a stream of air. The resulting solid was collected by filtration to yield 25.5 g of D-10. On further evaporation of the filtrate, additional 3.5 g of the product was obtained to give a total of 29 g (75% yield) of D-10, m.p. 52-54°. Recrystallization from Skelly F afforded pure D-10 as white needles, m.p. 54-56°.

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.45; N, 5.10; N, 6.45. Found: C, 66.31; H, 4.90; N, 6.43.

Ethyl 3-Methoxy-2-pyridineacetate (D-19)

To a stirred solution of 5.0 g (0.05 mole) of diisopropylamine in 100 ml of dry THF cooled in an ice-water bath was added dropwise 22 ml of 2.4 M BuLi in hexane (0.053 mole). Ten minutes after the addition, it was followed by the addition of 6.2 g (0.05 mole) of 3-methoxy-2-methyl-pyridine and the mixture was stirred for 40 min. The resulting red solution was transferred to a dropping funnel and added dropwise to a solution of 6 g (0.055 mole) of ethyl chloroformate in 150 ml of THF at -67 to -70°.

The solution was stirred and allowed to slowly warm to room temperature without removal of the cooling bath. After standing overnight, the cloudy solution was cleared by filtration and the filtrate evaporated to a paste. The latter was diluted in 50 ml of water and extracted with ether (3 x 50 ml). The ether extract was washed with saturated aqueous NaCl and dried (MgSO$_4$). Ether was removed and the resulting red liquid was distilled $\underline{in\ vacuo}$ through a 6-in. Vigreux column. The distillate collected at 30-45°/0.15-0.75 mm was discarded. The Vigreux column was then replaced by a short distilling head the distillation was continued. The fraction collected at 98-118°/0.15-0.2 mm was the desired compound D-19. It weighed 1.2 g (12% yield). NMR (CDCl$_3$): δ 1.21 ($\underline{t}$, J = 7 cps, 3H, -O-CH$_2$-CH$_3$), 3.80 ($\underline{s}$, 3H, OCH$_3$), 3.87 ($\underline{s}$, 2H, -CH$_2$- attached to the pyridine ring), 4.16 ($\underline{q}$, J = 7 cps, 2H, -O-CH$_2$-CH$_3$), 7.16 ($\underline{d}$, J = 3 cps, 2H, aro-Hs) and 8.13 ($\underline{t}$, J = 3 cps, 1H, aro-H). IR: 1740 cm^{-1} (strong, C = O), 1580 cm^{-1} (a medium pyridine ring absorption).

$\underline{Anal}$. Calcd. for C$_{10}$H$_{13}$NO$_3$: C, 61.51; H, 6.71; N, 7.18. Found: C, 61.63; H, 6.78; N, 7.21.

Ethyl 3-Methoxy-2-piperidineacetate (D-20)

A mixture of 2.5 g of D-19, 1 g of 5% Rh/C and 120 ml of absolute EtOH was hydrogenated in a Parr Hydrogenator under 64 psig of H$_2$ for 92 hr. Catalyst was removed by filtration and the filtrate evaporated under reduced pressure to give 3.2 g of D-20 as a liquid. The nmr and ir absorptions were in accord with the reduced product.

Ethyl 3-Methoxy-2-(N-acetyl)piperidineacetate (D-21)

The aforementioned crude product D-20, 3.1 g, was dissolved in 15 ml of Ac$_2$O and was allowed to stand at room temperature for 36 hr. The solution was diluted with 100 ml of water, extracted with ether (3 x 50 ml) and dried (MgSO$_4$). Evaporation of ether gave 1.3 g of D-21. IR: 1730 cm^{-1} (ester C = O), 1650 cm^{-1} (amide C = O). When the aqueous layer was basified with Na$_2$CO$_3$ and extracted with ether (3 x 50 ml), and additional 0.5 g of D-21 was obtained. Purification and identification of this product is in progress.

Diethyl Anilinomethylenesuccinate (D-26)

To diethyl formylsuccinate, prepared by sodium-catalyzed condensation of diethyl succinate and ethyl formate,[54] (14.1 g, 0.07 mole), was added in several portions, 6.5 g (0.07 mole) of aniline. The product crystal-

lized slowly after initial exothermic reaction subsided. It was filtered and washed with Skelly F to give 10 g of the desired product, m.p. 92-96°. On recrystallization from acetone-Skelly F, white prisms, m.p. 102-104°, were obtained.

Anal. Calcd. for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.05. Found: C, 65.22; H, 6.81; N, 5.20.

Ethyl 4-Hydroxy-3-quinolineacetate (D-27)

Diethyl anilinomethylenesuccinate (D-26), 27.6 g, was added drop-wise into 200 ml of Dowtherm preheated to 240°. After 30 min of heating at 240-250°, the mixture was allowed to cool The solid product was isolated by filtration (2.5g), m.p. 200-204°. It was recrystallized from methanol as offwhite crystals, m.p. 215-217°.

Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.68; H, 5.44; N, 6.09.

Ethyl 4-Chloro-3-quinolineacetate (D-28)

Ethyl 4-hydroxy-3-quinolineacetate (D-27), 4.6 g, was heated with 20 ml of $POCl_3$ on a steam bath for 3 hr. After cooling, the mixture was poured into ice water and made basic with ammonium hydroxide. The product solidified slowly and was isolated by filtration. There was obtained 4.5 g of the desired product as beige crystals, m.p. 65-67°. It may be recrystal-lized from methanol as beige needles, but the melting point becomes lower.

2-(2-Hydroxypropyl)-3-methoxypiperidine (D-36)

The method of Baker and McEvoy[40] was followed. A mixture of 48.8 g (0.29 mole) of 2-(2-hydroxypropyl)-3-methoxypyridine in 150 ml of absolute EtOH was hydrogenated at room temperature under 60 psig of H_2 in the presence of 16 g of 5% Rh/Al_2O_3. After 18 hr the mixture was heated at 60° and the hydrogenation was continued for an additional 4 hr. Catalyst was removed by filtration and the filtrate evaporated in vacuo to give 48 g (96% yield) of the crude product. Its nmr spectrum revealed that the product was contaminated by only a trace of unreduced starting material.

(2-Acetonyl-3-methoxy)piperidine (D-37)

        The aforementioned crude D-36 was dissolved in 310 ml of water. The solution was cooled at 0° and to it was slowly added, with stirring, 66 g of concentrated H_2SO_4 followed by portionwise addition of 35 g of $K_2Cr_2O_7$. The temperature throughout the addition was kept below 35°. The resulting dark green solution was stirred at room temperature for 40 hr. The precipitated purple solid was collected by filtration, washed with a small amount of water, and discarded. The filtrate was basified with 50% KOH to pH 11. The resulting dark green suspension was mixed with 100 g of Celite and filtered and the solid washed with 100 ml of water. The combined aqueous solution was extracted with ether (3 x 150 ml) and CH_2Cl_2 (3 x 150 ml). The organic extracts were dried ($MgSO_4$). Removal of ether yielded 5 g of a mixture of unreacted starting alcohol and the ketone D-37. From the CH_2Cl_2 extraction was obtained 25 g (50% yield) of the crude ketone D-37.

        According to Barringer et al.[42] the ketone D-37 obtained by the Baker's procedure[40] was in the cis-form D-37a. This could be isomerized into a mixture of trans-(D-37b) and cis-(D-37a) in a ratio of 7:3 by heating the liquid at 100° for 90 min. When 13 g of the crude D-37 was isomerized under the reported[42] reaction condition, 5.4 g of the 7:3 mixture was obtained after distillation, b.p. 74°/0.15 mm (lit.,[42] b.p. 88-93°/2.5 mm). The ir and nmr confirmed the structural assignment.

[N-Carboallyloxy-3-methyl-2-(3-bromo-2-oxopropyl)]piperidine (D-38b)

        To a solution of 5.4 g of D-37 in 22 ml of AcOH cooled in an ice bath was added 22 ml of 30% HBr/AcOH followed by addition of 1.6 ml of Br_2 in 5 ml of AcOH. The mixture was stirred overnight and the solvent evaporated in vacuo at 50°. The residual intermediate D-38a (ca 0.03 mole) was dissolved in 60 ml of $CHCl_3$, cooled at 0°, and neutralized with saturated aqueous $NaHCO_3$. To this was added simultaneously, with stirring, saturated aqueous $NaHCO_3$ and 4.8 g (0.04 mole) of allyl chloroformate at such a rate that the pH of the reaction solution was maintained between 7-8. After the addition the mixture was stirred at room temperature for 2 hr. The $CHCl_3$ layer was separated and the aqueous layer extracted twice with $CHCl_3$. The combined $CHCl_3$ solution was washed twice with 0.1 N HCl, twice with water, and dried ($MgSO_4$). It was evaporated in vacuo at 40° to give 90% yield of D-38b as an oil. This compound was used (see Results and Discussion Section) without further purification.

IV. COMPOUND SUBMITTED FOR BIOLOGICAL STUDIES

MO-482 (BE-16930; WB-11-15A):

Ethyl Tetrahydrothienyl-2-carboxylate
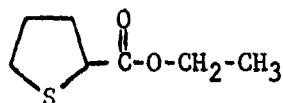
2.0 g

MO-483 (BE-16949; Y-I-51):

N-(4-Oxohexyl)phthalimide
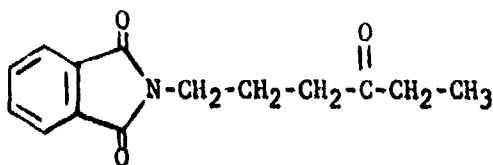
2.0 g

MO-484 (BE-16958; PC-VII-12):

α-p-Chlorobenzoyl-γ-butyrolactone
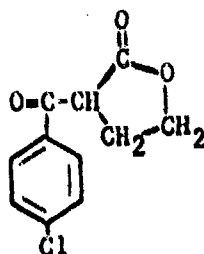
2.0 g

MO-485 (BE-16967; Y-I-79):

8-(6-Amino-3-hexylamino)-6-methoxy-4-methylquinoline
  Diphosphate Dihydrate
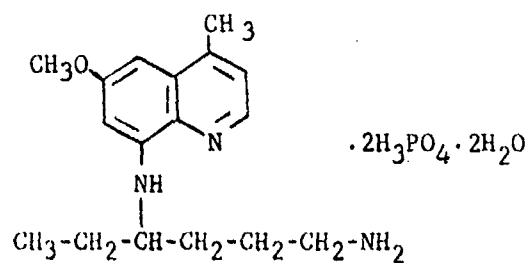
$\cdot 2H_3PO_4 \cdot 2H_2O$ 5.1 g

MO-486 (BE-17535; PC-VII-17):

α-Acetyl-α-(p-chlorobenzoyl)-γ-butyrolactone
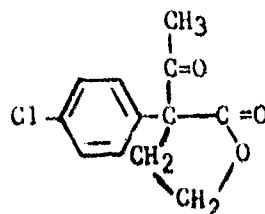
2.0 g

MO-487 (BE-17544; WB-11-40C):

N^1,N^1-Diethyl-N^4-(3,4-dimethoxyphenyl)-1,4-pentanediamine

5.0 g

60
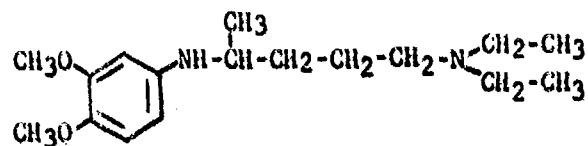
MO-488 (BE-17553; Y-I-82-2):

3-Methyl-2-furoic Acid
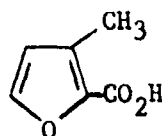
2.0 g

MO-489 (BE-17562; Y-I-85-1):

5-(3-Methyl-2-furyl)hydantoin
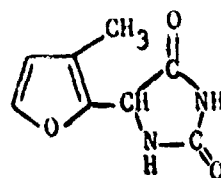
2.0 g

MO-490 (BE-17571; PC-VII-22):

4-Bromo-4'-chlorobutyrophenone

2.0 g

61
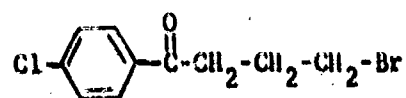
<u>MO-491(BE-18014; PC-VII-25)</u>:

2-(<u>p</u>-Chlorophenyl)tetrahydrofuran-2-carboxaldehyde Semicarbazone
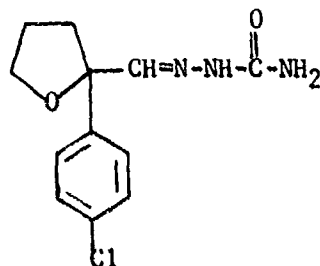
2.0 g

<u>MO-492(BE-18023; Y-I-90)</u>:

2-Amino-2-(3-methyl-2-furyl)acetic acid
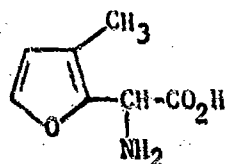
2.0 g

<u>MO-493(BE-18103; Y-I-94)</u>:

2-Amino-2-(3-methyl-2-tetrahydrofuryl)acetic acid

1.1 g
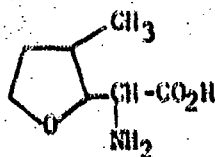
<u>MO-494(BE-19995; Y-I-95)</u>:

6-[(5-Diethylamino-2-pentyl)amino]quinoxaline

4.5 g

62
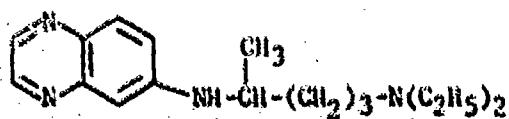
2-Methoxy-5-nitro-N-(1-phthalimido-4-pentyl)aniline
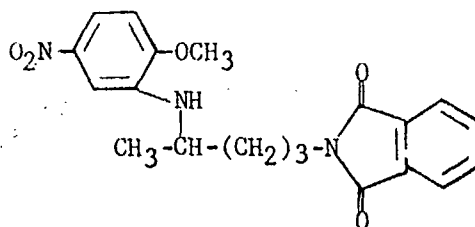
2.0 g

MO-496(BE-45128; Y-II-11):

6-(N-Acetamido)-7-methoxyquinoxaline
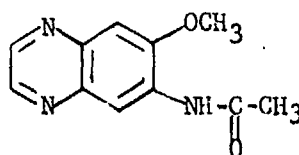
2.0 g

MO-497(BE-50030; Y-II-20):

6-[(5-Diethylamino-2-pentyl)amino]-7-methoxyquinoxaline
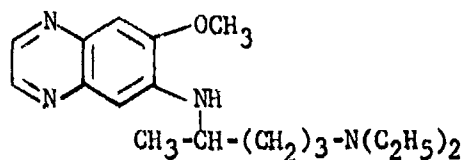
4.3 g

MO-498(BE-66387; Y-II-26):

2-Bromo-4,5-dimethoxy-N-(5-diethylamino-2-pentyl)aniline
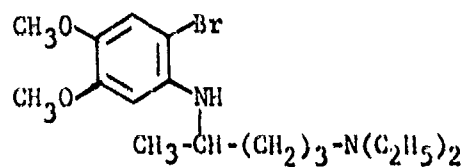
6.3 g

MO-499(BE-66458; Y-II-2):

4-Methoxy-2-nitroacetanilide
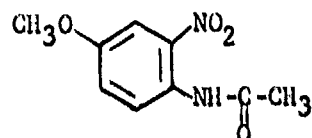
2.0 g

MO-500(BE-66467; Y-II-19):

2-Amino-4-methoxyacetanilide

CH_3O — NH_2, NH-C-CH_3, O
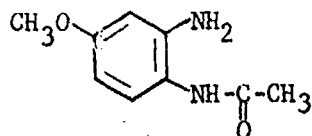
2.0 g

MO-501(BE-66476; Y-II-12):

4,5-Dinitro-2-methoxyacetanilide

CH_3O — NO_2, CH_3-C-NH — NO_2, O
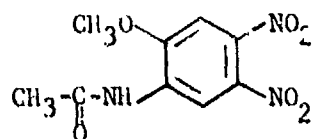
2.0 g

MO-502(BE-66485 ; Y-II-265; WB-11-67):

6-Bromo-3,4-dimethoxy-1-nitrobenzene

CH_3O — Br, CH_3O — NO_2
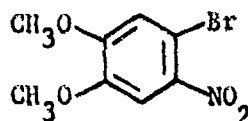
2.0 g

MO-503(BE-66798; PC-VII-40):

3-Acetamido-N-[(p-chloro-1-methyl)benzylidene]-4-methoxyaniline

CH_3O, CH_3-C-NH — CH_3, N=C — Cl, O
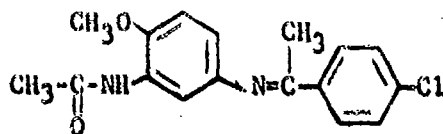
2.0 g

MO-504(BE-66805; Y-II-28):

4-Methoxy-2-nitrotrifluoroacetanilide

CH_3O — NO_2, NH-C-CF_3, O

2.0 g

64
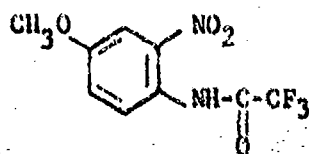
<u>MO-505(BE-55884; Y-II-49)</u>:

2-Bromo-4,5-methylenedioxy-N-(5-diethylamino-2-pentyl)aniline

$$CH_2O_2 \text{ ring} - C_6H_2(Br) - NH-CH(CH_3)-(CH_2)_3-N(C_2H_5)_2$$
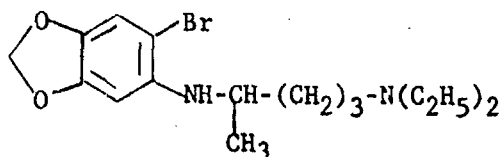
5.2 g

<u>MO-506(BE-57575; Y-II-28)</u>:

5-Methoxy-2-(trifluoromethyl)benzimidazole

$$CH_3O - \text{benzimidazole} - CF_3$$
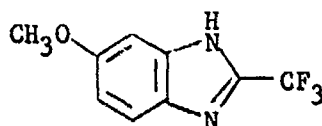
2.0 g

<u>MO-507(BE-57584; PC-VII-48)</u>:

Diethyl anilinomethylenemalonate

$$C_6H_5 - NH-CH=C(CO_2C_2H_5)_2$$
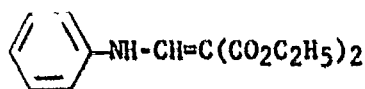
2.0 g

<u>MO-508(BE-58778; PC-VII-49)</u>:

Ethyl 4-hydroxy-2-quinolinecarboxylate

$$\text{quinoline}(OH) - CO_2C_2H_5$$
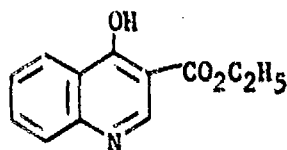
2.0 g

<u>MO-509(BE-58787; PC-VII-51)</u>:

Ethyl 4-chloro-2-quinolinecarboxylate

$$\text{quinoline}(Cl) - CO_2C_2H_5$$
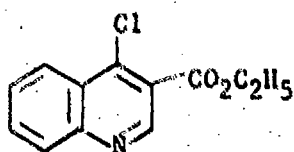
2.0 g

MO-510(BE-58796; Y-11-66):

N-Acetyldehydroleucine

$$CH_3-CH-CH=C-CO_2H$$
$$\quad\quad | \quad\quad\quad |$$
$$\quad CH_3 \quad\quad NH$$
$$\quad\quad\quad\quad\quad\quad |$$
$$\quad\quad\quad\quad\quad\quad CO-CH_3$$
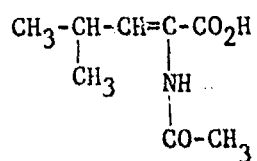
5.0 g

MO-511(BE-58803; Y-11-A):

2-Acetamidoacrylic Acid

$$CH_2=C-CO_2H$$
$$\quad\quad |$$
$$\quad\quad NH$$
$$\quad\quad |$$
$$\quad\quad CO-CH_3$$
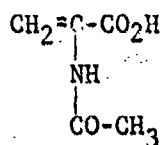
5.0 g

MO-512(BE-58812; Y-11-68):

2-(p-Chlorobenzamido)crotonic Acid

$$CH_3-CH=C-CO_2H$$
$$\quad\quad\quad\quad |$$
$$\quad\quad\quad\quad NH$$
$$\quad\quad\quad\quad |$$
$$\quad\quad\quad\quad C=O$$

Cl
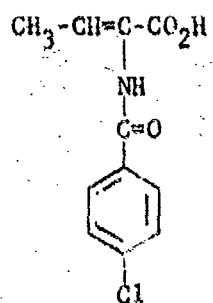
5.0 g

MO-513(BE-58821; Y-11-64):

N-(p-Chlorobenzoyl)-D,L-threonine

$$CH_3-CH-CH-CO_2H$$
$$\quad\quad\quad | \quad |$$
$$\quad\quad OH \quad NH$$
$$\quad\quad\quad\quad\quad |$$
$$\quad\quad\quad\quad\quad C=O$$

Cl
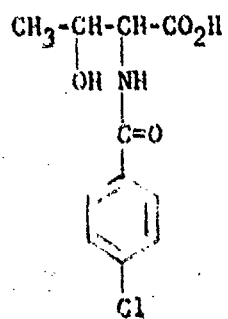
2.0 g

<u>MO-514(BE-58830; Y-11-63)</u>:

N-(Chloroacetyl)-<u>D</u>,<u>L</u>-leucine

$$CH_3-CH-CH_2-CH-CO_2H$$

$$\underset{CH_3}{|} \qquad \underset{NH}{|}$$

$$\underset{C=O}{|}$$

$$\underset{CH_2Cl}{|}$$
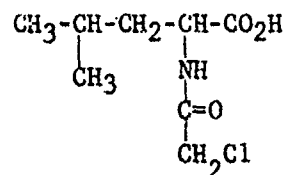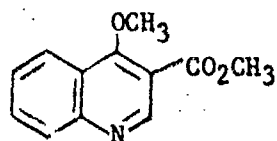
2.0 g

<u>MO-515 (BE-76061; PC-VII-53)</u>:
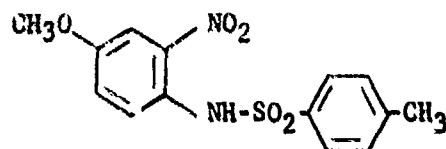
Methyl 4-Methoxy-3-quinolinecarboxylate

2.0 g

<u>MO-516 (BE-76070; WB-11-72A)</u>:
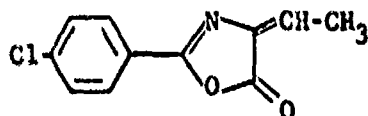
N-(2-Nitro-4-anisyl)-<u>p</u>-toluenesulfonamide
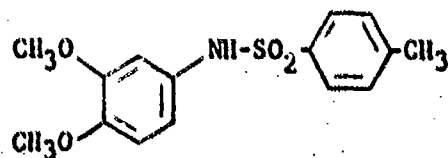

2.0 g

<u>MO-517 (BE-76089; Y-II-67)</u>:

2-(<u>p</u>-Chlorophenyl)-4-ethylideneoxazol-5-one
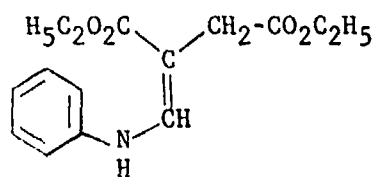

2.0 g

<u>MO-518 (BE-77817; BW-11-73B)</u>:

N-(3,4-Dimethoxyphenyl)-<u>p</u>-toluenesulfonamide

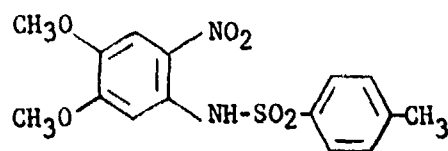2.0 g

67

MO-519 (BE-77826; PC-VII-58):

Diethyl Anilinomethylenesuccinate

$$H_5C_2O_2C-C(=CH-NH-C_6H_5)-CH_2-CO_2C_2H_5$$

2.0 g

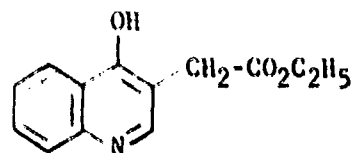MO-520 (BE-82756; WB-11-75B):

N-(4,5-Dimethoxy-2-nitrophenyl)-p-toluenesulfonamide

2.0 g

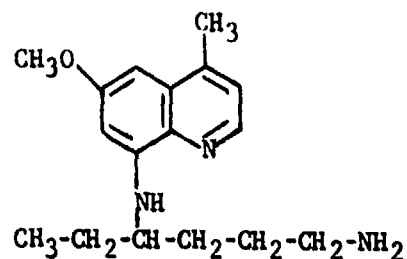MO-521 (BE-76034; PC-VII-59):

Ethyl 4-Hydroxy-3-quinolyacetate

2.0 g

V. ANTIMALARIAL TEST RESULTS

Among 40 compounds submitted for antimalarial activity evaluation, 8-(6-amino-3-hexylamino)-6-methoxy-4-methylquinoline diphosphate (WR-215761, BE-1696, MO-485) displayed outstanding activity against _Plasmodium berghei_.

WR-215761

This compound is active at 20 mg/kg, with five out of five cures at 320 mg/kg, and is nontoxic even at 640 mg/kg. A comparison of the activity of this compound with that of primaquine on the same _P. berghei_ system,[55,56] is listed as follows.

	Dosage (mg/kg)							
	5	10	20	40	80	160	320	640
Primaquine[55]	--	--	+2.2	+4.2	+6.4	+7.0 (2 toxic)	5 toxic	5 toxic
Primaquine[56]	--	--	+4.0	+5.0	+9.4	+10.8 (2 toxic)	5 toxic	5 toxic
WR-215761	+2.1	+4.1	+7.3	+7.9	+9.7	+11.5	5 cures	5 cures

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VII. PUBLICATIONS

Following is an up-to-date list of publications resulting from our work done in connection with the malaria study.

"3-Piperonylsydnone. A New Type of Antimalarial Agent," W. H. Nyberg and C. C. Cheng, J. Med. Chem., 8, 531-553 (1965).

"2,8-Bis(substituted amino)phenothiazine 5,5-Dioxides," P.-L. Chien and C. C. Cheng, J. Med. Chem., 9, 960-962 (1966). ARPM Publication No. 132.

"Structural Modification Studies of 3-Piperonylsydnone. I. Synthesis of Piperonyl-Substituted Pyrazoles, Isoxazoles, Triazoles, Oxadiazoles, and Thiadiazoles," S. G. Boots, and C. C. Cheng, J. Heterocyclic Chem., 4, 272-283 (1967). ARPM Publication No. 194.

"Synthesis and Antimalarial Evaluation of Some 1,7-Naphthyridines and 2,9-Diazaanthracenes," P.-L. Chien, and C. C. Cheng, J. Med. Chem., 11, 164-167 (1968). ARPM Publication No. 226.

"Pyrazoles I. Synthesis of 4-Hydroxypyrazolo[3,4-d]-v-triazine. A New Analog of Hypoxanthine," C. C. Cheng, R. K. Robins, K. C. Cheng, and D. C. Lin, J. Pharm. Sci., 57, 1044-1045 (1968). ARPM Publication No. 257.

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"1,5-Naphthyridines: Synthesis of 7-Chloro-4-(4-diethylamino-1-methyl-butylamino)-2-methoxy-1,5-naphthyridine and Related Compounds," D. J. McCaustland and C. C. Cheng, J. Heterocyclic Chem., 7, 467-473 (1970). ARPM Publication No. 741.

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"Structural Modification Studies of 3-Piperonylsydnone. III. Some Analogs of 3-Piperonylsydnone and 2,4-Diamino-5-piperonylpyrimidine," D. J. McCaustland, W. H. Burton, and C. C. Cheng, J. Heterocyclic Chem., 8, 89-97 (1971). ARPM Publication No. 876.

"Structure and Antimalarial Activity of Aminoalcohols and 2-(p-Chlorophenyl)-2-(4-piperidyl)tetrahydrofuran," C. C. Cheng, J. Pharm. Sci., 60, 1590-1598 (1971). ARPM Publication No. 928.

"Structure-Activity Relationship Studies on Antimalarial Phenanthrene Amino Alcohols. Modification of the Side Chain," P.-L. Chien, D. J. McCaustland, W. H. Burton, and C. C. Cheng, J. Med. Chem., 15, 28-33 (1972). ARPM Publication No. 958.

"Synthesis of Three ^{14}C-Labeled Phenanthrene Aminomethanols," P.-L. Chien and C. C. Cheng, Mikrochim. Acta, 401-412 (1973). ARPM Publication No. 1078.

"Further Side Chain Modification of Antimalarial Phenanthrene Amino Alcohols," P.-L. Chien and C. C. Cheng, J. Med. Chem., 16, 1093-1096 (1973). ARPM Publication No. 1008.

"Deaza Analogs of Some 4-, 6-, and 8-Aminoquinolines," D. J. McCaustland, P.-L. Chien, C. C. Cheng, J. Novotny, W. L. Schreiner, and F. W. Starks, J. Med. Chem., 16, 1311-1314 (1973). ARPM Publication No. 1201.

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"Difference in Antimalarial Activity Between Certain Aminoalcohol Diastereomers," P.-L. Chien and C. C. Cheng, J. Med. Chem., in press. ARPM Publication No. 1353.

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